Drug-Induced Liver Injury (DILI) including Acetaminophen (APAP) 2014: Practical Tips

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Aim: Discuss Clinical Trends in DILI and Acetaminophen Liver Injury

Topics:
• Overall scope of the problem
• Problems in diagnosis
• Issues regarding causality
• Acetaminophen clinical tips
• Treatment of DILI/APAP

Number of DILI Articles Published Annually, currently >1200

Etiology of Acute Liver Failure in the USA
Adult Registry (n = 2,000)

ALF Study Group, Jan 2013
The Conundrum of Idiosyncrasy: Why are just a few patients susceptible?

“idio-sug-krasia” (Hippocrates, ~ 400 B.C.)

idios (ἰδιός) - one’s own, self
syn (σύν) - together
krasis (κρασί) - mixing, mixture

a person’s own individual mixture of characteristics, factors; uniqueness

It does NOT mean rare, unexpected, unexplained, although it may or may not be any or all of them!

### Features of Idiosyncratic Drug Reactions

1. Occur rarely, not really dose related
2. Similar consistent pattern for each drug
3. Similar drugs exhibit similar features, “class effects”
4. Individual drugs in a class still vary considerably
5. Reactions occur at varying time intervals after ingestion (3 days to one year)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Use</th>
<th>Regulatory Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ximelagatran</td>
<td>Anticoagulant</td>
<td>Not approved (2006)</td>
</tr>
<tr>
<td>Telithromycin</td>
<td>Antibiotic</td>
<td>Restricted Use (2007)</td>
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</tbody>
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Adapted from: Kaplowitz, Nat Rev Drug Disc 2005

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### Features of Idiosyncratic Drug Reactions

6. Reactions vary in severity, but typically severe and fatal if drug continued
7. Mild injury often disappears with continued use (adaptation)
8. Rarity of most reactions suggests multiple hits
9. Re-challenge is virtually always met with greater severity, shorter latency
10. Most drugs causing idiosyncrasy are at doses >100 mg/day
Drugs causing cholestasis

- More than one case report:
  - Amoxicilliin/clavulanate
  - Carbamazepine
  - Erythromycin esters
  - Flucloxacillin
  - Methyltestosterone
  - Phenytoin
  - Prochlorperazine
  - Trimethoprim/sulfa

- Less frequent:
  - Azathioprine
  - Barbiturates
  - Captopril
  - Allopurinol
  - Clindamycin

Black cohosh hepatotoxicity: autoimmune hepatitis

35 yo woman, began a mail order pill one/day. Admitted 4 wks later with coma. TB 19.3, AST 835/ALT 674, INR 3.9, ANA 1:640. Transplantation required.
Genomes will help solve the riddle of idiosyncrasy

Techniques will vary from directed SNP analyses to GWAS

There may be relatively few ‘susceptibility MHC haplotypes’

Still, much complexity will likely remain:

- Initial susceptibility: MHC haplotype PLUS
- Downstream modulation (e.g., IL-10 genes)

<table>
<thead>
<tr>
<th>HLA-DRB1<em>0101 and HLA-DRB1</em>0701</th>
<th>Hypersensitivity/hepatotoxicity</th>
<th>abacavir</th>
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<td>lamivudine</td>
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<td>stavudine</td>
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<tr>
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<td>Hypersensitivity/hepatotoxicity</td>
<td>zidovudine</td>
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<th>Hypersensitivity/hepatotoxicity</th>
<th>efavirenz</th>
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<td>Hypersensitivity/hepatotoxicity</td>
<td>indinavir</td>
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<td>Hypersensitivity/hepatotoxicity</td>
<td>ritonavir</td>
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<td>Hypersensitivity/hepatotoxicity</td>
<td>darunavir</td>
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**Causality Assessment**

- How do we know a drug has caused the injury?
- Answer: Guilt by association
- RUCAM, a rudimentary tool for determining causality
- Better systems are needed!

**Components of RUCAM**

(Roussel Uclaf Causality Assessment Method)

Points awarded for the following categories:
1. Time to onset
2. Course, “dechallenge”
3. Risk factors (age, alcohol, pregnancy)
4. Concomitant drugs
5. Search for non-drug causes
6. Previous information on hepatotoxicity of the drug
7. Response to re-administration

Problems: too little data, inter/intra-observer variation, Inclusion of non-valid parameters

**Basic Steps in Causality**

Most injury is to hepatocytes: determine is it ‘hepatitis’?

- Measure aminotransferases and are they new?
- Assess severity: level of ALT, INR, encephalopathy
- What are other possible causes? Alcohol, Viral, Ischemia, (gall)Stones = “AVIS.”
- What (other) drugs are being taken?
- What is likelihood of each drug?

Hyman Zimmerman, MD 1914-1999
The spectrum of severity
(suspect drugs provide ‘signals’)

- Percent with ALT elevations higher than comparators: 3X ULN, 5X ULN, 10X ULN
- Occurrence of Hy’s Law cases (jaundice)
- Occurrence of acute liver failure

\[
\begin{align*}
\text{ALF} \\
\text{Hy’s Law} \\
\text{ALT 5X ULN} \\
\text{ALT 3X ULN}
\end{align*}
\]

DILIN Causality (Likelihood) Score, given by percent

1 = **Definite**: >95% Liver injury is typical for the drug or herbal product (‘signature’ or pattern of injury, timing of onset, recovery). The evidence for causality is ‘beyond a reasonable doubt’

2 = **Highly likely**: 75–95% The evidence for causality is ‘clear and convincing’ but not definite

3 = **Probable**: 50–74% The causality is supported by ‘the preponderance of evidence’ as implicating the drug but the evidence cannot be considered definite/highly likely.

4 = **Possible**: 25–49% The causality is not supported by ‘the preponderance of evidence’; however, one cannot definitively exclude the possibility

5 = **Unlikely**: <25% The evidence for causality is ‘highly unlikely’ based upon the available information

6 = **Insufficient data**

DILIN: US NIH-sponsored network 2003-2018

https://dilin.dcriduke.edu/

Problems with RUCAM and DILIN

**RUCAM**
1. Full data rarely available
2. Dechallenge often cannot be determined
3. Risk factors (age, alcohol) unwarranted
4. Good people still get different scores!

**Bottom line**: Lacks accuracy!

**DILIN**
1. Expert opinion requires ‘experts’!
2. Impractical/takes time
3. Has better data /good inter-observer consistency
4. Is useful for establishing phenotype for genetics

**Bottom line**: Lacks day to day clinical utility!
**Most frequent DILI agents in adults**

<table>
<thead>
<tr>
<th></th>
<th>ALFSG</th>
<th>DILIN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>INH (w/wo rif/pyraz)</td>
<td>25</td>
<td>28</td>
</tr>
<tr>
<td>Sulfa (TMP/SMX, sulfasalazine)</td>
<td>12</td>
<td>8</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>11</td>
<td>23</td>
</tr>
<tr>
<td>Azoles</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>Amox/Clavulanate</td>
<td>0</td>
<td>37</td>
</tr>
<tr>
<td>Others</td>
<td>13</td>
<td>115</td>
</tr>
<tr>
<td>Anti-convulsants</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phenytoin</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Others including psychotropics</td>
<td>10</td>
<td>43</td>
</tr>
<tr>
<td>NSAIDS</td>
<td>7</td>
<td>21</td>
</tr>
<tr>
<td>Herbs</td>
<td>14</td>
<td>59</td>
</tr>
</tbody>
</table>

**Transplant-free survival by etiology and coma grade**

Coma grade I-II patients had ~50% better survival than III-IV

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**Review: Key Steps in DILI**

- Call it hepatitis (or some other form)
- Look HARD for the specific drugs
- Make sure the temporal relationship fits
- Rule out ‘AVIS’
- Think about specific drug patterns and consult livertox.nih.gov
- Think like an expert!

**Summary of this talk; additional points**

- Causality assessment is a black art, not a science
- Think outside your comfort zone of hepatocellular injury—it is not all INH and TMP/SMX!
- Vanishing bile ducts due to antibiotics
- Vascular injury yielding nodular regenerative hyperplasia
- Autoimmune hepatitis due to biologics
- Congestive heart failure due to chemotherapy
  - Best advice
- Use livertox.nih.gov as your source for good info
Acetaminophen (Paracetamol) Hepatotoxicity

- Dose-related toxin
- Popular (mild) pain reliever
- Dwarfs all other forms of acute liver injury
- Largest selling OTC product/largest Rx generic
- Multi-billion dollar product/well-protected brand
- >100,000 calls annually to poison control centers
- 400+ deaths annually in the US, similar in EU
- Iconic model for studying liver injury
- Keeps basic scientists and clinicians employed!

Historical highlights I: Recognizing APAP problem

- 1960’s Acetaminophen (paracetamol) first used in UK
- 1966: First reports of hepatotoxicity
- 1970’s Becomes common analgesic/suicide agent in UK
- 1973 Mitchell and Jollow outline mechanism of injury
- 1975 Rumack develops nomogram to predict toxicity
- 1977 First report of NAC to prevent/manage toxicity
- 1986 Seeff and Zimmerman: association with alcohol—‘Therapeutic misadventure’ described in US
**Parkland Hospital study of APAP overdoses**

<table>
<thead>
<tr>
<th>Suicidal: n=50</th>
<th>Unintentional: n=21</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Suicide admitted</td>
<td>• Suicide denied</td>
</tr>
<tr>
<td>• Single time point</td>
<td>• Several days’ use</td>
</tr>
<tr>
<td>• No cause of pain</td>
<td>• Reason for pain</td>
</tr>
<tr>
<td>• Early presentation</td>
<td>• Late presentation</td>
</tr>
<tr>
<td>• 20% ALT &gt; 1,000</td>
<td>• Virtually all high ALT</td>
</tr>
<tr>
<td>• 1 ALF/death in 50 (2%)</td>
<td>• 8 ALF; 6 (29%) died</td>
</tr>
</tbody>
</table>

Schiedt et al., NEJM 1997:337:1112-17

Only 9 of 71 had ALF, but they were mostly unintentional.

**Acute Liver Failure Study Group: based at UTSW**

Rationale: Network to study a rare disease

- Began in 1998, 15 adult, 10 pediatric sites
- 2,300 cases in adult, ~1,100 in pediatric registry
- New added definition: ALI—INR > 2.0/no enceph
- Three directions:
  - Prospective clinical data, sera, plasma, DNA, tissue
  - Numerous ancillary studies in progress
  - Therapy trials: NAC trial done, STOP-ALF in progress

Funding: NIDDK U-01 through 2015

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**Cytochromes P450 lead to unstable compounds!**

- Nontoxic Metabolites
- NAPQI (highly reactive intermediate)
- Hepatocyte Damage
- Covalent binding to cell proteins, including enzyme itself
- Adducts
- Engagement of apoptosis?
- CYP?

Mitchell DR, Jollow DJ, et al 1973, JPET
### Comparison of Different ALF Etiology Groups

<table>
<thead>
<tr>
<th></th>
<th>APAP</th>
<th>Drug</th>
<th>Indeterminate</th>
<th>HepA/HepB</th>
<th>All Others</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=916</td>
<td>n=220</td>
<td>n=245</td>
<td>n=36/142</td>
<td>N=441</td>
</tr>
<tr>
<td>Age (median)</td>
<td>37</td>
<td>46</td>
<td>39</td>
<td>45/43</td>
<td>45</td>
</tr>
<tr>
<td>Sex (% F)</td>
<td>76 %</td>
<td>69 %</td>
<td>59</td>
<td>44/44</td>
<td>71</td>
</tr>
<tr>
<td>Jaundice to coma (Days)</td>
<td>1</td>
<td>11.5</td>
<td>11</td>
<td>4/8</td>
<td>7</td>
</tr>
<tr>
<td>Coma 33 (%)</td>
<td>53</td>
<td>35</td>
<td>48</td>
<td>56/52</td>
<td>38</td>
</tr>
<tr>
<td>ALT (median IU)</td>
<td>377</td>
<td>639.5</td>
<td>865</td>
<td>2275/1649</td>
<td>681</td>
</tr>
<tr>
<td>Bili (median)</td>
<td>4.3</td>
<td>19.8</td>
<td>21.1</td>
<td>12.3/18.4</td>
<td>13.3</td>
</tr>
<tr>
<td>Tx (%)</td>
<td>9</td>
<td>40</td>
<td>42</td>
<td>33/38</td>
<td>32</td>
</tr>
<tr>
<td>Spontaneous Survival (%)</td>
<td>66</td>
<td>24</td>
<td>22</td>
<td>50/21</td>
<td>31</td>
</tr>
<tr>
<td>Overall Survival (%)</td>
<td>73</td>
<td>58</td>
<td>60</td>
<td>72/55</td>
<td>58</td>
</tr>
</tbody>
</table>

### Treatment for APAP Overdose

**N-acetylcysteine (NAC) is an effective antidote!**

- IV NAC will totally prevent toxicity if given < 12 hrs
- Uncertain benefit after 30 hours
- Supportive care in ICU: may develop fatal complications: brain edema.
- Initial evaluation: is it ALF? If so, is he/she a LT candidate? If so, consider early transfer to liver transplant center.

### Ornithine Phenyl Acetate: STOP-ALF Trial

**Lower ammonia to manage cerebral edema**

- Ammonia is the putative cause for cerebral edema
- OPA traps ammonia and allows renal excretion
- Could be used prophylactically or as treatment
- IV, few side effects, might work in cirrhosis also
- ALFSG is studying the acetaminophen ALF/ALI group since July 2012—to be completed 2014.

### Several studies highlight role of NH₃ in raising ICP

OCR-002 Uses Physiological Pathways to Eliminate Nitrogen

Lee WM, Jalan RV. Gastroenterology 2009

Phenacetyl-CoA : Gln acyltransferase

Goran Klintmalm, Baylor University Med Ctr, Dallas

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2000 Patients enrolled
761 (38%) listed
Spontaneous survivors N=864 (43%)
Transplanted N=482 (24%)
Died (Not Transplanted) N=654 (33%)
Alive N=410 (85%)
Died N=72 (10%)

Overall survival: N=1274 (64%)

ALFSG data, 1998-2012

928 APAP patients enrolled
233 (25%) listed
Spontaneous survivors N=616 (66%)
Transplanted N=82 (9%)
Died (Not Transplanted) N=204 (22%)
Alive N=61 (74%)
Died N=8 (10%)

Overall survival: N=677 (73%)

ALFSG data for APAP, 1998-2012
APAP Hepatotoxicity: Summary

- Still an important problem dwarfing DILI!
- Opioid compounds involved in 40+
- Comprises 18% of indeterminate ALF
- Frequent psych issues and drug abuse in both groups
- Multiple products important in at least 20%, more in pain patients.
- Renal injury is common in APAP
- Still the largest cause of death from ALF in US

Overall Summary: DILI and APAP 2014

- Identifying drug-induced hepatotoxicity is vital
- Bad outcomes can and do occur
- Key here is taking a great history
- Loyal patients sometimes hurt themselves
- Be aware of agents that cause toxicity and alert to new ones. Use Livertox.nih.gov to look things up
- OSU is a good source for information and consultation: we specialize in handling patients with Acute Liver Failure!!