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Drugs, Chemicals, Hepatotoxins: Is it the Substance or the Person?

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Disclaimer

• The opinions or assertions presented herein are the private views and opinions of the authors and are not to be construed as conveying either an official endorsement or criticism by the US Department of Health and Human Services, the Public Health Service, or the Food and Drug Administration.
Known Facts

• DILI:
  – a major concern in medical practice and public health
  – the leading cause of acute liver failure in the world
  – major cause for drug failure in clinical trials
  – usually considered idiosyncratic
  – until 1997, it was the leading cause for withdrawal of an FDA-approved drug – 8 WDs; 4 for liver failure*

• Incidence:
  – 14-19/100,000 in general population**
  – 30-35/100,000 using EMR data*** – under-reported?

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* http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/ucm071471.htm
Data Through January 2014

![Graph showing the etiology of acute liver failure in the USA Adult Registry (n = 2,102).](image)

*Etiology of Acute Liver Failure in the USA Adult Registry (n = 2,102)*

- APAP: 974 cases (46%)
- Drug: 227 cases (11%)
- Hep B: 147 cases
- Hep A: 37 cases
- Autoimm: 144 cases
- Ischemic: 117 cases
- Wilson's: 26 cases
- Budd-Chiari: 15 cases
- Pregnancy: 18 cases
- Other: 145 cases
- Indeter: 252 cases

*ALF Study Group, Jan 2014*
## Drugs Approved in 1997 and Subsequently WD for Liver Failure

<table>
<thead>
<tr>
<th>Established Name Proprietary Name / Sponsor</th>
<th>Intended Use Toxicity</th>
<th>Approval Date</th>
<th>WD Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Troglitazone Rezulin / ParkeDavis</td>
<td>Diabetes Fatal liver failure</td>
<td>01/29/97</td>
<td>05/01/02</td>
</tr>
<tr>
<td>Bromfenac Duract / Wyeth</td>
<td>Analgesic Fatal liver failure</td>
<td>07/15/97</td>
<td>07/03/03</td>
</tr>
<tr>
<td>Trovafloxacin Trovan / Pfizer</td>
<td>Antibiotic Liver Failure</td>
<td>12/18/97</td>
<td>03/09/05</td>
</tr>
<tr>
<td>Alatrofloxacin Trovan IV / Pfizer</td>
<td>Antibiotic Liver failure</td>
<td>12/19/97</td>
<td>03/09/05</td>
</tr>
</tbody>
</table>
The Fundamental Questions

• Is it a toxic drug?

OR

• An especially susceptible person?

• How can a rare problem be the leading cause of acute liver failure, more than all diseases combined?
Additional Facts

• The same drug may be quite safe for most people, but quite toxic for a few*
  – Severity
  – Consequences
  – Time course
  – Degree of causal likelihood

• The liver has an amazing capacity to recover from injury**
  – Regrows if 2/3 resected - regenerates rapidly if hepatocytes are killed or removed
  – Alters the activities of enzymes – changes itself, “adapts” to injurious effects

* Senior, J.; Antitargets and Drug Safety; 2014 (in press)
**Bucher, NL (1967), NEJM
Problem Drugs and Individual Risk Factors

- Identification of either is always challenging!
- Dose and properties of drugs impact initial cellular damage
- Host factors drive susceptibility as well as repair
- Idiosyncrasy of the host is responsible for many of the cases of DILI after marketing*

* Senior, J. : Antitargets and Drug Safety; 2014 (in press)
Thoughts from Hy Zimmerman

- There are a variety of chemical agents that induce hepatotoxicity
  - inorganic
  - organic
- “Natural” substances can also be problematic
- The potential for producing injury is arranged along a spectrum, modified by a number of variables and involving several different mechanisms
Problem Drugs and Individual Risk Factors

• Risks in humans likely determined by multiple factors:
  – Drug properties
  – Patient attributes
  – DILI mechanisms
Drug Properties Related to DILI

• Threshold dose
• Lipophilicity
  – Affects cellular uptake
  – Affects ADMET (absorption, distribution, metabolism, excretion, and toxicity)
• Reactive metabolites
• Oxidative stress
• Mitochondrial liability
Prediciting Serious Liver Injury: Challenges

- Biomarkers are not specific enough
- Negative rechallenge is unconvincing
  - - - for rare events
- Positive rechallenge is powerful but dangerous
- Difficult to determine causality
As I Have Listened, I Ask, and You Should Continue to Ask…

• What makes certain people respond better to the same dose and regimen of the same drug than do others?
• What makes certain people susceptible to serious adverse effects, when most people aren’t?
Listen carefully to the speakers who follow ---

• They will be touching on many of these points