Drug Induced Hepatitis

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Importance of Drug Hepatotoxicity

- Major cause of acute liver failure
- Mimics all forms of acute or chronic liver disease
- Leading cause of failures in drug development and postmarking “black-box” warnings and withdrawals
Clinical-Pathological Signature of DILI

**Acute Injury**
- Hepatocellular *(hepatitis)*
  
  (acetaminophen, INH)
- Cholestatic / mixed
  
  (erythromycin, sulindac)
- Others – HVOD *(chemo)*
  
  microvesicular fat
  
  (NRTI, valproate)

**Chronic Injury**
- Chronic hepatitis
  
  (methyldopa, nitrofurantoin, minocycline, diclofenac, germander)
- Ductopenic cholestasis
  
  (rare, after acute)
- NASH
  
  (amiodarone, methotrexate, tamoxifen)
- Nodular Regen. Hyperplasia
  
  (thiopurines)
Important Facts About Drug-Induced Liver Disease

1. The bulk of adverse hepatic drug reactions present with an acute hepatitis, cholestasis or mixed signature. Although some drugs present a narrow signature, others have a very broad signature.

2. Acute drug hepatitis with jaundice is life threatening (10% mortality) (Hy’s Law)

3. Cholestatic reactions resolve slowly and can lead to chronic ductopenia (cirrhosis rare)

4. Diagnosis is guilt by association: temporal (latency, dechallenge), exclusions (rechallenge, record, risk factors, systemic allergic features).
**Chronicity After Acute DILI**

**Definition:** Abnormalities for > 3 months after cessation for hepatocellular and > 6 months for cholestatic damage.

Idiosyncratic DILI in Spanish Registry (Andrade, Lucena et al)

493 cases → 5.7% chronic

- 28 pts — 18 cholestatic mixed (9%)
- 10 hepatocellular (4%)
- 1 cirrhosis
- 2 ductopenia
- 3 cirrhosis
- 2 chronic hepatitis

- Slow resolution?
- “Heal” into cirrhosis?
- Trigger underlying autoimmune hepatitis
Predictability of Toxicity

1. Predictable – dose-related, frequent injury, few examples

2. Unpredictable – ±dose-related, low incidence (idiosyncratic) (0.01 – 1.0%) superimposed on higher incidence of mild asympt. injury
   • Allergic – fever, rash, eosinophilia, autoantibodies
     1 – 4 week latency, (+) rechallenge
   • Non-allergic – absence of immune features, often long latency (up to 1 year)
# Acute Allergic DILI

**Allergic features:** Fever, rash, eosinophilia, lymphadenopathy, characteristic initial latency (1-4 weeks) and rapid rechallenge response

**Clinical Signature:**

<table>
<thead>
<tr>
<th>“Hepatitis”</th>
<th>Cholestatic / Mixed</th>
</tr>
</thead>
<tbody>
<tr>
<td>allopurinol</td>
<td>ACE inhibitors</td>
</tr>
<tr>
<td>haloalkane anesthetics</td>
<td>amoxicillin – clavulanic acid</td>
</tr>
<tr>
<td>propylthiouracil</td>
<td>phenytoin</td>
</tr>
<tr>
<td></td>
<td>sulfonamides</td>
</tr>
<tr>
<td></td>
<td>sulindac</td>
</tr>
<tr>
<td></td>
<td>(+/− ALF)</td>
</tr>
<tr>
<td></td>
<td>erythromycins</td>
</tr>
<tr>
<td></td>
<td>phenothiazines</td>
</tr>
</tbody>
</table>

**Pathological:** eosinophilic infiltration and/or granuloma; cholangiolitis and vanishing ducts (chronic)
# Autoimmune Hepatitis-like DILI

**Clinical**
- Systemic allergic manifestations less prominent
- Sometimes very long latency (minocycline, nitrofurantoin, diclofenac)
- Although most cases are acute, some cases are chronic, even leading to cirrhosis
  - Low grade ongoing injury with continued use
  - Asymptomatic until sudden late presentation

**Autoimmune phenomena**

<table>
<thead>
<tr>
<th>Anti-CYP</th>
<th>ANA, ASMA, ↑γγ</th>
</tr>
</thead>
<tbody>
<tr>
<td>dihydralazine</td>
<td>oxyphenisatin</td>
</tr>
<tr>
<td>tienilic acid</td>
<td>diclofenac</td>
</tr>
<tr>
<td></td>
<td>methyldopa</td>
</tr>
<tr>
<td></td>
<td>minocycline</td>
</tr>
<tr>
<td></td>
<td>nitrofurantoin</td>
</tr>
</tbody>
</table>
Acute Liver Failure (death, OLT)

Overt Liver Disease (symptoms, jaundice)

Mild Injury (reverses with continued use – “adaptation”)

All Patients ➔ Subgroup (1.0 – 10%) ➔ Subgroup (0.1 – 1.0%) ➔ Subgroup (0.01 – 0.1%)

ALT > 3 x ULN

Idiosyncratic Hepatotoxicity

Acute Liver Failure (death, OLT)
# Idiosyncratic Hepatotoxicity in Clinical Trials

<table>
<thead>
<tr>
<th></th>
<th>Troglitazone</th>
<th>Bosentan</th>
<th>Ximelagatran</th>
</tr>
</thead>
<tbody>
<tr>
<td>ULN</td>
<td>(2500)</td>
<td>(658)</td>
<td>(6948)</td>
</tr>
<tr>
<td>ALT &gt; 3x</td>
<td>1.8%</td>
<td>12 – 14%</td>
<td>7.8%</td>
</tr>
<tr>
<td>ALT &gt; 10x</td>
<td>0.6%</td>
<td>2.7%</td>
<td>1.9%</td>
</tr>
<tr>
<td>ALT &gt; 8x Bili &gt; 3x</td>
<td>0.08%</td>
<td>0.3%</td>
<td>0.1%</td>
</tr>
<tr>
<td>Fatal ALF</td>
<td>0</td>
<td>0</td>
<td>0.04%*</td>
</tr>
</tbody>
</table>

*3 cases (1 HBV)
Pathogenesis of DILI

Hepatocytes (upstream)

Parent Drug
- mitochondria
- Reactive metabolite
- covalent binding
- oxidative stress

Stress Cell Death (mild)

Adaptive Immune Response

hapten

Innate Immune System (downstream)

Cytokines
- Chemokines
- ROS, RNS

NK / NKT
- Kupffer
- PMNs

NK / NKT
- Pro-inflammatory

PMNs
- Anti-inflammatory

Pro-inflammatory

OVERT LIVER INJURY

Anti-inflammatory

REPAIR RECOVERY
## Importance of Reactive Metabolites in Liver Injury

The diagram illustrates the pathway from DRUG to reactive metabolite, then to covalent binding, oxidative stress, and finally detoxification, leading to cytotoxicity or allergy. Reactive metabolites can be formed through the action of cytochrome P450 (CYP) enzymes. The list of drugs and their metabolites points out the potential risks associated with each drug.

### Withdrawn Drugs
- Benoxaprofen
- Flutamide
- Iproniazid
- Nefazodone
- Tienilic acid
- Troglitazone
- Bromfenac

### Warning Drugs
- Acetaminophen
- Carbamazepine
- Clozapine
- Dacarbazine
- Dantrolene
- Diclofenac
- Disulfiram
- Felbamate
- Halothane
- Isoniazid
- Leflunomide

### Not Approved in the U.S.
- Alpidem
- Aminoptine
- Amodiaquine
- Cincophen
- Dihydralazine
- Dilevalol
- Ebrotidine
- Troglitazone
- Bromfenac
- Flutamide
- Iproniazid
- Nefazodone
- Tienilic acid
- Troglitazone
- Bromfenac

*black box (adapted from Walgren et al. Crit Rev Toxicol 2005;35:325)
Acetaminophen: The Most Widely Studied Hepatotoxin

• No animal models of allergic or nonallergic idiosyncratic hepatotoxicity
• Knowledge of mechanisms of acetaminophen toxicity provides insights which may be applied to idiosyncrasy
• Can acetaminophen be considered an idiosyncratic hepatotoxin in the unintentional overdose or therapeutic setting?
# Acute Liver Failure Surveillance: 610 Cases

<table>
<thead>
<tr>
<th>Category</th>
<th>Percentage</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen</td>
<td>43%</td>
<td>&gt; 1/2 unintentional</td>
</tr>
<tr>
<td></td>
<td></td>
<td>~ 1/6 therapeutic doses</td>
</tr>
<tr>
<td>Other Drugs</td>
<td>13%</td>
<td></td>
</tr>
<tr>
<td>Indeterminate</td>
<td>15%</td>
<td>? acetaminophen</td>
</tr>
<tr>
<td>Viral Hepatitis</td>
<td>11%</td>
<td>? acetaminophen</td>
</tr>
<tr>
<td>Autoimmune</td>
<td>6%</td>
<td></td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>12%</td>
<td>(Lee et al.)</td>
</tr>
</tbody>
</table>
Unmasking Acetaminophen (APAP) Toxicity

- 25% of indeterminate ALF cases had protein-cysteine-S-NAPQI in serum. (Davern et al., Gast 130:687, 2006)
- 12.5% of acute viral hepatitis ALF have adducts - ? worsen. (Polsen et al., Gast 130:A-772, 2006)
The Effect of Acetaminophen on Serum ALT in Healthy Subjects

4 g/day x 14 days

<table>
<thead>
<tr>
<th>ALT</th>
<th>APAP* (n=126)</th>
<th>Placebo (n=39)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 3X ULN</td>
<td>40%</td>
<td>0</td>
</tr>
<tr>
<td>&gt; 5X ULN</td>
<td>26%</td>
<td>0</td>
</tr>
<tr>
<td>&gt; 8X ULN</td>
<td>8%</td>
<td>0</td>
</tr>
</tbody>
</table>

- 4 equal groups: APAP alone or combined with oxycodone, hydromorphone, morphine
- Stop when 3X ULN; no abnormalities until day 4

(Watkins, Kaplowitz, Slattery et al., JAMA, 2006)
Effect of Daily Therapeutic APAP on Serum ALT: A Representative Case
Hepatocellular Mechanisms of APAP Toxicity

APAP → NAPQI → covalent binding → lethal oxidative stress
↓\[\text{GSHm}\]

nonlethal oxidative stress

Nrf-2 → protection

JNK (sustained) → injury
Effect of Stress Kinase Inhibitors on APAP Hepatotoxicity \textit{in vivo} in C57/BL6 Mice

- APAP 800mg/kg
- APAP + JNK-Inh. *p<0.01

- APAP 1000mg/kg
  - n=6

- APAP + JNK-Inh.  
  - n=6

- APAP + p38-Inh.  
  - n=6

- APAP + ERK-Inh.  
  - n=6

Serum ALT

- % Survival

- Hours: 0, 12, 24, 36, 48
Protection by Delayed Administration of JNK Inhibitor

Serum ALT at 24 hrs

Time of JNK inh injection (hr)
APAP given at time zero
Effect of JNK1+2 Knockdown (antisense) on Acetaminophen Toxicity

![Serum ALT (U/L) graph]

Control antisense  JNK1+2 antisense  APAP + control antisense

APAP + JNK1+2 antisense

800 mg/kg
Role of the Innate Immune System in Susceptibility to Acetaminophen

Protection
- IFNγ knockout
- Fas antisense
- NK / NKT depletion

Worsening
- IL-10 knockout
- IL-6 knockout

Acetaminophen → NAPQI → Covalent binding → GSH

Cytokine/chemokine balance
Depletion of NK / NKT Cells Protects Against APAP

A) Serum ALT

B) Survival

C) Hepatic GSH

D) Histology

Control  APAP  APAP+αNK1.1
Working Model of Innate Immune System in APAP Toxicity

APAP → Hepatocyte Stress + Necrosis → Kupffer cell TLR 4 → chemokines → NK / NKT ligands → NK / NKT cells → IFNγ, Osteopontin, FasL

LIVER INJURY → Inflammation
Emerging Hypothesis for Pathogenesis of Idiosyncratic DILI: Lessons From Acetaminophen

DRUG → Reactive metabolite → stress → Activation of signal transduction and transcription → resistant hepatocytes → recovery

massive disruption

limited cell death or release of stress signals

sensitized hepatocytes → severe DILI

Innate immune response → recovery