Management of Drug-induced Liver Injury (DILI)

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“Poisons and medicines are oftentimes the same substance given with different intents.”

Peter Mere Latham
1878
Importance of Drug-Induced Liver Injury

• The liver is a major target organ for serious adverse effects of drugs
• Major cause of fulminant hepatic failure
• Drugs are a frequent cause of undiagnosed liver disease
• DILI is most common reason for post marketing withdrawal of medications
Classification of DILI

• **Direct (intrinsic) hepatotoxicity**
  – Usually dose-related
  – Short interval between ingestion and evidence of toxicity
  – Reproducible in animal models

• **Idiosyncratic hepatotoxicity**
  – Not always dose-related
  – Usually not reproducible in animal models
  – Host factors play important role in risk
Direct Hepatotoxicity: Acute Necrosis

- Marked elevation in ALT and AST
- Elevated bilirubin indicates severity
- Prolonged INR if severe
- Examples include acetaminophen, cocaine, niacin, ecstasy, some chemotherapeutic agents, IV amiodarone; L-asparaginase
- Differential: ischemia, hypothermia
Direct Hepatotoxicity: Lactic Acidosis, Microvesicular Steatosis

- Nausea, anorexia, fatigue
- Minimal elevation of AST and ALT
- Elevation of lactate, INR, ammonia
- Stavudine, didanosine, linezolid, IV tetracycline, aspirin (Reye’s)
- Differential: inherited mitochondrial dysfunction
Idiosyncratic Drug Reactions

- Metabolic idiosyncrasy
  - Metabolism of drugs triggers “anti-stress” and antioxidant defense mechanisms in cells
  - These responses may differ between individuals leading to toxicity

- Immunologic idiosyncrasy
  - Genetically determined
  - Aspects of hypersensitivity
Clinical Spectrum of Idiosyncratic DILI

- Hepatocellular injury
  - Acute necrosis
  - Chronic hepatitis
  - ALT > 2-3 X ULN & ALT/alk phos ratio > 5

- Intrahepatic cholestasis
  - Alk phos > 2X ULN & ALT/alk phos ratio < 2

- Mixed cholestatic/hepatocellular injury
  - ALT & Alk phos > 2 X ULN & ratio >2 & < 5
Frequency of Idiosyncratic Drug Reactions

<table>
<thead>
<tr>
<th>Incidence</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-20/1000</td>
<td>INH chlorpromazine, dantrolene</td>
</tr>
<tr>
<td>1-5/10,000</td>
<td>Estrogens, Amoxicillin-Clavulanate</td>
</tr>
<tr>
<td>0.5-5/10,000</td>
<td>Ketoconazole</td>
</tr>
<tr>
<td>1-10/10,000</td>
<td>Diclofenac, sulindac, phenytoin,</td>
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<tr>
<td></td>
<td>nitrofurantoin, dicloxacillin</td>
</tr>
<tr>
<td>1-10/100,000</td>
<td>Minocycline</td>
</tr>
<tr>
<td>2/1,000,000</td>
<td>Statins</td>
</tr>
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</table>
Frequency of DILI

- Overall occurrence of serious hepatotoxicity is 2/10,000
- **Drug-Induced Liver Injury Network (DILIN)** formed by NIH in 2007 to determine frequency of idiosyncratic hepatotoxicity
- First 1000 cases: 84% prescription meds, 16% herbal/dietary supplements; top 10 = 36%
Top 10 Causes of Idiosyncratic DILI

1. Amoxicillin-clavulanate
2. Isoniazid*
3. Nitrofurantoin*
4. TMP-SMX
5. Minocycline
6. Cefazolin
7. Azithromycin*
8. Ciprofloxacin*
9. Diclofenac*
10. Levofloxacin*

*If jaundiced, fatality rate > 10%
all are older drugs approved before 2000
Newer Drugs in Top 50 DILI Cases

- Duloxetine
- Rosuvastatin
- Telithromycin
- Imatinib
- Atomoxetine
- Oxaliplatin
- Flavocoxid
Herbal and Dietary Supplements

• 16% of all cases of hepatotoxicity
• Anabolic steroids—bland cholestasis
• Other—many cause acute necrosis, inflammation
Drug-Induced Cholestasis

- Cholestasis may occur with or without associated inflammation, e.g. estrogens
- Cholestatic drug reactions are usually self-limited, but a small percentage may progress to vanishing bile-duct syndrome
- Initial severity is predictor of progression
- Injury is thought to involve canalicular membrane transporters
Amoxicillin/Clavulanate Hepatotoxicity
Cholestatic Liver Damage Due to Amoxicillin/Clavulanate

- Amoxicillin/clavulanic acid is one of the most commonly prescribed antibiotics for URI
- Mild, reversible elevation of ALT is noted in 2-3% of those treated
- Serious hepatotoxicity occurs with an incidence of 1:56-78,000 prescriptions written
- Hypersensitivity features including rash and eosinophilia are seen in 40-60%
- Associated with particular HLA haplotypes: DRB1*07:01-DQB1*03:03; DRB1*15:01-DQB1*06:02
Deaths associated with underlying co-morbidity
- Transplant pts had high ALT and bilirubin
- Those with chronic DILI had higher ALT, bilirubin, longer duration and more severe DILI at presentation

*One subject died after liver transplant
Etiology of Acute Liver Failure

- Acetaminophen: 47%
- Drugs: 11%
- HBV: 7%
- HAV: 3%
- Ischemia: 4%
- Autoimmune: 5%
- Wilson: 2%
- Indeterminate: 14%
- Other: 7%


n = 1,147
Drug-Induced Acute Liver Failure

- Drugs account for more than 50% of ALF in U.S. (Acute Liver Failure Study Group)
- 40% of ALF was due to acetaminophen toxicity, of which 55% were unintentional
- 13% of ALF was due to idiosyncratic DILI
- Survival was lowest in those with idiosyncratic DILI
# Acute Liver Failure Outcomes

<table>
<thead>
<tr>
<th></th>
<th>APAP (916)</th>
<th>DILI (220)</th>
<th>Indeterm (245)</th>
<th>HBV (147)</th>
<th>Other (134)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ALT</strong></td>
<td>3773</td>
<td>640</td>
<td>865</td>
<td>1650</td>
<td>681</td>
</tr>
<tr>
<td><strong>Bilirubin</strong></td>
<td>4.3</td>
<td>19.8</td>
<td>21.1</td>
<td>18.4</td>
<td>13.9</td>
</tr>
<tr>
<td><strong>Transplant</strong></td>
<td>9%</td>
<td>40%</td>
<td>42%</td>
<td>39%</td>
<td>32%</td>
</tr>
<tr>
<td><strong>Survival w/o TX</strong></td>
<td>63%</td>
<td>24%</td>
<td>22%</td>
<td>55%</td>
<td>31%</td>
</tr>
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</table>

Severe Acetaminophen Hepatotoxicity

Acetaminophen Metabolism

APAP Sulfate

35%

APAP Glucuronide

55%

10%

P4502E1

NAPQI

GSH

NAPQI-GSH Adducts
Acetaminophen Toxicity

APAP Sulfate 35%  APAP Glucuronide 55%

NAPQI 10%  P4502E1

Apoptosis & cytokine release

Covalent binding to macromolecules

GSH depletion

NAPQI-GSH Adducts
Management of Suspected Acetaminophen Toxicity

- Plasma levels of acetaminophen are only helpful within the first 24 hrs after suspected ingestion
- Initiate treatment with oral N-Ac, 140 mg/kg as a loading dose followed by 70 mg/kg every 4 hrs for 72 hrs
- IV N-Ac may be given (300 mg/kg) by continuous infusion over 20 hrs
- Supportive care including fluids, antibiotics pressors, acid suppression as needed
NAC for Treatment of Non-APAP ALF

• 173 patients with non-ischemic, non-APAP, acute liver failure randomized to IV NAC

• DILI (45); indeterminate (41); HBV (37) AIH (26)

• Transplant-free survival was 58% vs 27% for DILI and 40% vs 23% for indeterminate in treated group

• Overall, transplant-free survival 40% v 27% (p=.04)

• Only patients with Grade 1-2 coma showed benefit

Drug-Induced Liver Injury Summary

• Most drug-induced liver injury is idiosyncratic and unpredictable
• A wide spectrum of clinical and histological manifestations may result from DILI
• Underlying liver disease may predispose to injury from some, but not all drugs
• A high index of suspicion is needed to diagnose drug-induced liver injury
Diagnosis of DILI

- Time of onset and resolution of symptoms/signs of liver disease in relation to drug ingestion
- Re-challenge is seldom, if ever, indicated and may potentially be hazardous
- Exclude other possible disorders since DILI often mimics other liver diseases
Management of Drug-Induced Liver Injury

- Stop administration of offending drug
- Generalized use of corticosteroids is not warranted
- Ursodiol (15 mg/kg) may be helpful in those with cholestatic liver damage
- N-acetylcysteine helps APAP toxicity and may be of benefit for other drugs causing ALF