Drug Induced Liver Injury

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Palm Springs, CA

Case

- 28 year old white male
- PMHx Grave’s disease; Rx levothyroxine 175 mcg
- No recent travel
- Feeling feverish Jan 2-3, took acetaminophen
- Developed nausea/vomiting x a few days, then tea-colored urine
- HAV IgM negative at urgent care
- Self referred to GI Jan 12: bilirubin = 9, sent to ED

Case

- In ED:
  - Jaundice, oriented without asterixis
  - Endorsed use of herbals Kratom x 3days (12/31-1/2) and (later) Kava for the past year to help with focus and anxiety
  - Denied other drug use
  - Social alcohol use, later acknowledged heavy (6-10) new year’s eve drinking
  - No other herbals/supplements
  - No other medications
  - No raw fish/shellfish
Overview: Drug Induced Liver Injury (DILI)

- Epidemiology
- General principles of drug metabolism
- Mechanisms and risk factors
- Classification
- Common examples of drug hepatotoxicity
- DILI Network

Epidemiology

- Relatively uncommon (1/10,000 to 1/100,000 subjects who take the drug)
- Leading cause of acute liver failure in the United States
- Single most common adverse drug reaction
- Mimics acute and chronic liver disease
- Most DILI resolves with drug discontinuation
- Prescription, herbal and over-the-counter dietary supplements and medications
- Difficult to identify high risk patients
  - Underlying chronic liver disease
  - Cofactors (e.g.: alcohol, supplements)

Etiology of Acute Liver Failure

US Adult Registry (n=1,321)

More than half of all US ALF is drug-related

Since 1998
Establishing Drug as Causative Agent

- Temporal profile
- Manifestation of liver toxicity has variable time course
- Liver enzymes abnormalities can persist for months
- Systematic literature search for each drug
- Rechallenge
- Exclude other diseases
- Extrahepatic features can point to immunoallergy
- Consider drug levels, liver biopsy

Drug Metabolism

- Drugs rendered hydrophilic by biochemical processes in the hepatocyte
- Hepatic biotransformation involves oxidative pathways, primarily by cytochrome P-450
- Hydrophilic product exported into plasma or bile by transport proteins located on the hepatocyte membrane
- Excreted by the kidney or the gastrointestinal tract

Hepatic Drug Metabolism

Phase I
- CYP
- Transferases
- ROS
- Hepatic Injury

Phase II
- Active Metabolite
- Conjugated Drug
- Excretion
Classification of DILI

- Predictable vs. idiosyncratic hepatotoxins
- Direct toxins vs. immune mediated
- Allergic vs. Nonallergic
- Acute vs. chronic
- Liver test abnormalities:
  Hepatocellular vs. cholestatic vs. mixed
- Histologic features:
  granulomatous, steatotic, vascular

Clinical Classification of DILI

<table>
<thead>
<tr>
<th>Predictable Hepatotoxins</th>
<th>Idiosyncratic Hepatotoxins</th>
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</thead>
<tbody>
<tr>
<td>Dose Dependent</td>
<td></td>
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<tr>
<td>Reproducible in Other Species</td>
<td>Yes</td>
</tr>
<tr>
<td>Incidence</td>
<td>High</td>
</tr>
<tr>
<td>Latency to Injury</td>
<td>Short (hours)</td>
</tr>
<tr>
<td>Extrahepatic involvement</td>
<td>Usually absent</td>
</tr>
<tr>
<td>Response to rechallenge</td>
<td>variable</td>
</tr>
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</table>

Clinical Patterns of DILI

- Hepatocellular
- Cholestasis
- Granulomatous
- Microvesicular fat
- Steatohepatitis
- Autoimmune
- Fibrosis
- Vascular collapse
- Oncogenesis
- Mixed
Hepatocellular

- Marked elevations in serum aminotransferases
- Usually precedes increases in total bilirubin and modest increases in alkaline phosphatase

[Image: Acute hepatitis with hepatocellular swelling, inflammation and disarray of hepatic lobule]

Hepatocellular

- Acarbose
- Acetaminophen
- Amiodarone
- Isoniazid
- Ketoconazole
- Rifampin
- Tetracyclines
- Trazodone
- Methotrexate
- NSAIDs
- Statins

[Image: 34yo with tylenol overdose- severe centrilobular necrosis with sparing of portal tracts and periportal hepatocytes]

Cholestasis

- Increase in alkaline phosphatase
- Precedes or are relatively more prominent than increases in transaminases
- More prolonged jaundice after drug withdrawal

[Image: Bile stained hepatocyte, cellular swelling and minimal inflammation]
Examples of DILI

<table>
<thead>
<tr>
<th>Signature disease</th>
<th>Drugs causing the feature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute hepatitis</td>
<td>Acetylsalicylic, bromfenac, etodolac, nabumetone, nonsteroidal, triflusal</td>
</tr>
<tr>
<td>Chronic hepatitis</td>
<td>Diclofenac, diclofenac, methylparax, minocycline, nifedipine</td>
</tr>
<tr>
<td>Acute cholestasis</td>
<td>ACE inhibitors, amoxicillin/cefiximic acid, chlorpromazine, erythromycin, sulfasalazine</td>
</tr>
<tr>
<td>Mixed pattern or atypical hepatitis</td>
<td>Phenytoin, sulfonamides</td>
</tr>
<tr>
<td>Nonalcoholic steatohepatitis</td>
<td>Gemfibrozil, zanaflex</td>
</tr>
<tr>
<td>Fibrosis/ormosis</td>
<td>Methotrexate</td>
</tr>
<tr>
<td>Microvesicular steatosis</td>
<td>NRTIs, valproic acid</td>
</tr>
<tr>
<td>Veno-occlusive disease</td>
<td>Busulfan, cyclophosphamide</td>
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</table>

Note: ACE, angiotension-converting enzyme; NRTI, nucleoside reverse transcriptase inhibitor.

Hy's Law

- Drugs causing acute hepatocellular injury and jaundice are associated with a mortality rate of approximately 10% (range of 5-50%)
- Validated by studies from Spain and Sweden

Percentage of patients with DILI progressing to liver transplantation and/or death

[Graph showing percentage of patients with DILI]

Mechanisms of DILI

- Immune-mediated attack on the liver
- Biochemical effect of toxic metabolites leading to loss of cell viability

[Graph showing mechanisms of DILI]
Six Mechanisms of DILI

- Cell membrane rupture
- Cholestasis
- Drug adducts (2)
- Apoptosis
- Mitochondrial function


Risk Factors for DILI

- Age (i.e. INH toxicity > 40, Reye’s syndrome < 3)
- Female gender
- Nutritional status- obesity and malnutrition
- Genetic factors (i.e. halothane)
- Concomitant medications
- History of drug reactions
- Alcohol consumption
- Underlying liver disease and co-morbidities

Examples of Drug Hepatotoxicity

<table>
<thead>
<tr>
<th>Category</th>
<th>Examples</th>
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<tr>
<td>Dose related</td>
<td>Acetaminophen</td>
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<tr>
<td>Metabolic idiosyncrasy</td>
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<td>Anticonvulsants</td>
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| Cholestatic                  | Antibiotics
|                              | Oral contraceptives                           |
| Chronic hepatitis/Fibrosis   | Methotrexate                                  |
| Vascular/VOD                 | Chemotherapeutic agents                       |
| Granulomatous                | Allopurinol                                   |
| Steatohepatitis              | Hydralazine                                   |
| Chronic w/autoantibodies     | Quinine                                       |
|                             | Amodarone                                     |
|                             | Nitrofurantoin                                |
Dose dependent toxicity:
Acetaminophen
- Minimal hepatotoxic dose 7.5g in adults
- Severe toxicity/fatal doses >15g
- Biochemical signs of liver damage in 24 to 48 hours
- Centrilobular necrosis
- Risk of toxicity correlates with plasma acetaminophen level (after 4 hours) and time after ingestion
- Late presentation or treatment (>12 hrs) associated with poor outcome

Dose dependent toxicity:
Acetaminophen
- Intentional (suicidal)
  - Single time point
  - Accounts for 42%
- Unintentional (pain relief)
  - Several days
  - Accounts for 49%
- In the UK and Europe 80% are intentional
- Mostly women (75%) and whites (85%)

Apparent causes of toxicity due to acetaminophen
1. Willful overdose (suicidality)
2. Lack of awareness of acetaminophen’s potential for toxicity
3. Unrecognized use of more than one acetaminophen preparation
4. Addiction to the opioid leading to excessive dosing
5. Failure to keep track because of clouded sensorium (other drugs/alcohol)
6. Acetaminophen’s alleged reputation for safety
7. Clouded sensorium due to concomitant drugs worsening outcomes
Acetaminophen Toxicity: Treatment

- Activated charcoal within 4 hours of ingestion
- Administer NAC within 8 hours post ingestion
- Oral N-Acetylcysteine: 140mg/kg loading followed by 70mg/kg q 4hrs x 72 hrs
- IV NAC: 150 mg/kg loading x 1 followed by 12.5 mg/kg/hr over 4 hrs, 6.25 mg/kg/hr over 16 hrs
- Supportive care/transplant for cases of FHF

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Isoniazid

- Mechanism: metabolic idiosyncrasy
- High frequency: 6-21 per 1000 of exposed persons
- Mortality 5-10%
- Increased risk/severity with age > 35 or <5 alcohol
- In combination (rifampicin, pyrazinamide, APAP)
- Hepatitis B/C
- Pregnancy
- Malnutrition
- Genetic variations
Isoniazid

• ALT abnormalities:
  -10-36% in the first 10 weeks
  -typically resolve spontaneously
  -okay to continue INH if LFT’s < 5x normal
• Hepatitis develops after latency period
  — 1 week-6 mo.
• Prodrome symptoms of fatigue, malaise, n/v
• Cases associated w/fatal outcome
  — longer duration of therapy
  — continued intake after onset of symptoms
• Most deaths from INH are preventable
• LFT monitoring- monthly initially, watch for clinical symptoms

Phenytoin

• Severe acute drug hepatitis: 1 in 10,000
• Onset: 1-8 weeks
• Mortality rate: 10-40%

• Clinical features (pseudomononucleosis syndrome):
  fever
  rash (exfoliative dermatitis)
  internal organs (kidney, lung, liver) involved
  leukocytosis, eosinophilia
  lymphadenopathy

Examples of Drug Hepatotoxicity

Dose related
Metabolic idiosyncrasy
Immunology
Cholestatic
Chronic hepatitis/Fibrosis
Vascular
Granulomatous
Steatohepatitis
Chronic w/autoantibodies

Acetaminophen
Isoniazid
Anticonvulsants
Antibiotics
Oral contraceptives
Methotrexate
Chemotherapeutic agents
Allopurinol
Hydralazine
Quinine
Amiodarone
Nitrofurantoin
Amoxicillin/Clavulanic Acid

- Most frequently reported antibiotic associated with DILI
- Estimated risk of symptomatic hepatitis: 1 in 100,000
- Clavulanic acid component probably responsible
- Typically produces a cholestatic hepatitis
- Delayed symptom onset: 1 to 8 weeks
- Strong association with HLA haplotype DRB1*1501-DRB5*0101-DQB1*0602, suggesting immunologic idiosyncrasy

Amox/Clav DILI: Prognosis

- 69 patients with Amoxicillin-Clavulanate Hepatotoxicity, Spanish registry
- Half of cases presented after cessation of therapy (mean 15, range 2-55 days)
- 2.9% overall rate of severe outcome (death/liver transplant)

Other antibiotics

- Cephalosporins
  - Few reports of hepatotoxicity
  - Biliary sludge associated with ceftriaxone
- Quinolones
  - Relatively safe, with exception of trovafloxacin
- Sulfonamides
  - Immunoallergic toxicity (rash, fever, eosinophilia)
  - Cholestatic hepatitis
- Macrolides (erythromycin, azithromycin, clarithromycin)
  - Cholestatic hepatitis, rash/eosinophilia
  - Acute liver failure with telithromycin (Ketek)
- Antifungals
  - Most common with ketoconazole
  - Asymptomatic LFT elevations frequent
- Minocycline, nitrofurantoin
  - Autoimmune hepatitis/SLE-like syndrome
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Drug Induced Fibrosis: Methotrexate

- Dose dependent promoter of hepatic fibrosis
- Avoidance of daily dosing, limitation of weekly doses to 5-15 mg decreases risk
- Increased risk with ETOH, DM, obesity
- Monitor LFTs; however fibrosis can develop in absence of LFT abnormalities
- Consider liver biopsy after 4g of MTX or 2 years of treatment

Veno-occlusive Disease

- Hepatic venous outflow obstruction from nonthrombotic occlusion of terminal hepatic venules and small intrahepatic veins due to endothelial damage
- BMT patients- alkylating chemotherapy
- Onset 2-10 weeks after starting therapy
- Sx’s: abdominal pain, hepatomegaly, progression to acute liver failure
- Resembles Budd Chiari except for patency of large hepatic veins on imaging
- No specific treatment, prognosis poor
Antiretroviral-associated liver injury

- Determining the incidence of DILI is difficult due to combination therapy
- Incidence is influenced by presence of host risk factors (HBV, HCV, alcohol)
- Elevated LFT’s in HIV infected patients may reflect other etiologies besides drug hepatotoxicity
- All classes of antiretrovirals have been associated with hepatic injury

Protease Inhibitors

- Hepatotoxicity with ritonavir
  - Low dose (<200mg BID) less hepatotoxic than previously used higher/boosted doses
- Unconjugated hyperbilirubinemia
  - Indinavir (Crixivan) and atazanavir (Reytaz)
- Severe hepatotoxicity
  - Tipranavir (Aptivus)

Nucleoside Reverse Transcriptase Inhibitors (NRTI)

- May be associated with lactic acidosis and microvesicular hepatic steatosis
- Mechanism: mitochondrial toxicity
- Early NRTI’s (AZT, ddi, d4T)
  - mostly asymptomatic LFT abnormalities
  - ~5% rate of serious hepatotoxicity
- Newer NRTI’s (lamivudine, abacavir, tenofovir) associated with much lower incidence (<1%) of hepatotoxicity
Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI)

- Nevirapine (Viramune), efavirenz (Sustiva), delavirdine (rescriptor)
- Nevirapine: rash associated hypersensitivity; rare cases of hepatotoxicity reported. Increased risk with HBV/HCV coinfection and higher CD4 counts/post exposure prophylaxis regimens.

HAART Considerations in Patients with Liver Disease

- HCV: didanosine-ribavirin: lactic acidosis; zidovudine-ribavirin: anemia
- HBV: HBV flares following discontinuation of emtricitabine, lamivudine, tenofovir
- Liver transplant: PI/NNRTI’s induce P450-> lower FK dose requirement; watch for sudden decrease in FK level after stopping HAART; avoid use of certain NRTI’s {ddC, ddl, d4T}

Case

<table>
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<tr>
<th>Baseline Labs</th>
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<tbody>
<tr>
<td>Total Protein = 7.2</td>
</tr>
<tr>
<td>Total Bil = 12.1</td>
</tr>
<tr>
<td>AST = 73</td>
</tr>
<tr>
<td>ALK Prol = 181</td>
</tr>
<tr>
<td>INR = 0.9</td>
</tr>
</tbody>
</table>

- Ultrasound was unremarkable
- AP was admitted
Case

Day 1 Labs
Total Protein = 7.3 7.7 Albumin = 4.4 4.1
Total bill = 12.1 15.5↑ Direct Bill = 9.2 10.3↑
AST = 73 64 ALT = 265 182
ALK Phos = 181 165 LDH =
INR = 0.9 1.0 GGT = 226

Case

Day 2 Labs
Total Protein = 7.3 7.7 7.2 Albumin = 4.4 4.1 3.8
Total bill = 12.1 15.6↑ 15.6 Direct Bill = 9.2 10.1↑ 10.1↑
AST = 73 64 54 ALT = 265 182 156
ALK Phos = 181 165 162 LDH = — — 189
INR = 0.9 1.0 GGT = 226

• Discharged home

Case

• Seen in outpatient follow up one week later
• Still jaundiced, itchy, no n/v f/c
• Labs drawn elsewhere 4 days post d/c
• Started ursodiol and diphenhydramine
Case

Follow up Labs

<table>
<thead>
<tr>
<th>Test</th>
<th>Value 1</th>
<th>Value 2</th>
<th>Value 3</th>
<th>Value 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Protein</td>
<td>7.3</td>
<td>7.7</td>
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</tr>
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<td>Albumin</td>
<td>4.4</td>
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<td>3.8</td>
<td></td>
</tr>
<tr>
<td>Total bil</td>
<td>12.1↑</td>
<td>15.5↑</td>
<td>15.6↑</td>
<td>18↑</td>
</tr>
<tr>
<td>Direct Bil</td>
<td>9.2</td>
<td>10.3↑</td>
<td>10.1↑</td>
<td>11↑</td>
</tr>
<tr>
<td>ALT</td>
<td>91</td>
<td>116</td>
<td>15.8↑</td>
<td></td>
</tr>
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<td>AST</td>
<td>73</td>
<td>64</td>
<td>54</td>
<td>42</td>
</tr>
<tr>
<td>ALP</td>
<td>181</td>
<td>165</td>
<td>162</td>
<td>221</td>
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<tr>
<td>LDH</td>
<td>—</td>
<td>—</td>
<td>189</td>
<td>185</td>
</tr>
<tr>
<td>INR</td>
<td>0.9</td>
<td>1.0</td>
<td>GGT</td>
<td>226 63</td>
</tr>
</tbody>
</table>

- Recommended return to the ED
- Refused
- Endorsed restricting fluids (read this on the internet)

Case

- Seen again 3 weeks later
- "No fat" diet = 2.5 kg weight loss/3 weeks
- Increased Ursodiol dose

Follow up 1 and 2 Labs

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Thank You