Drug-Induced Hepatocholestatic Injury

Laura Murphy, BSc.Phm.
Pharmacy Resident
ICU Rotation
The Hospital for Sick Children

Objectives
- Review clinical presentation of drug-induced liver injury
- Identify potential hepatotoxic /cholestatic medications
- Evaluate causality assessments
- Apply knowledge to our patient

Terminology
- ALF = acute liver failure
- ALT = alanine aminotransferase
- Alk Phos = alkaline phosphatase
- AST = aspartate aminotransferase
- DILI = drug-induced liver injury
- GGT = gammaglutamyltransferase
- LFT = liver function test
- RUCAM = Roussel Uclaf Causality Assessment Method

Patient SA
- 4 year old male
- Dilated cardiomyopathy
  - Respiratory distress & cardiac failure on ward
- Admit to ICU
  - Berlin Heart (May 1/07)
- Heart Transplant List
- Hepatomegaly

Drug Related Problems
- Sedation, pain management, BP management
  - Fatigue, lethargy, drowsiness
- Anticoagulation
  - Fibrin clots
- Antimicrobial therapy
  - Persistent fevers, hx of positive cultures
- TPN
  - Nutrition
- Electrolyte supplementation
- Increased liver enzymes
  - Caused by drug therapy/disease?

Medications
- Acetaminophen
- Lorazepam
- Chloral Hydrate
- Diazepam
- Codeine
- Clonidine
- Furosemide
- Spironolactone
- Propranolol
- Diprydamole
- Warfarin
- Heparin
- Omega 3 fatty acids
- TPN
- Lipids
- Omeprazole
- Ursodiol
- Calcium carbonate
- Magnesium sulfate
- Potassium chloride
- Sodium chloride
- Tazocin
- Vancomycin
- Amphotericin B
- Electrolytes
- CNS
- CVS
- Anticoagulation
- Antimicrobials
How can we assess hepatic injury?

- Liver Transaminases
  - AST
  - ALT
- Alkaline Phosphatase
- GGT
- Bilirubin
  - Conjugated
  - Unconjugated

In our patient:
- INR... anti-coagulated
- Albumin... supplemented
- Platelets... supplemented

**AST**

**ALT**

**GGT**

**Alk Phos**

**Bilirubin - Unconjugated**
**Histology of the Liver**

**Lab Tests – Review**

<table>
<thead>
<tr>
<th>Description</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin</td>
<td>Synthesized in the liver, indicator of liver function (also a marker of nutrition)</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>Chemical breakdown product of hemoglobin Elevated unconjugated: pre-hepatic damage/cholestasis Elevated conjugated: intra-hepatic damage/necrosis</td>
</tr>
<tr>
<td>INR</td>
<td>Liver synthesizes vitamin K dependent clotting factors, indicator of liver function</td>
</tr>
<tr>
<td>Platelets</td>
<td>Hepatic disease may cause splenomegaly- inc. trapping of platelets in the spleen/inc. bleeding</td>
</tr>
</tbody>
</table>

**Pathophysiological Mechanisms**

- Hepatitis (hepatocellular/cytotoxic)
- Cholestatic
- Vascular
- Neoplastic

**DRUG-INDUCED HEPATOCHOLESTATIC INJURY**
Pathophysiological Mechanisms

- Hepatitis
  - Idiosyncratic reactions
    - Formation of free radicals, ROS
  - Immune related
    - Production of adducts or haptens that migrate to cell membranes
    - Antibody mediated cytotoxicity may occur with secondary cytokine response and neutrophil mediated toxicity
      - Anti-liver/kidney microsomal (LKM)-targets CYP 2C9
      - Anti-liver antibody – targets CYP 1A2

- Steatosis
  - Accumulation of fatty acids in the mitochondria

- Cholestasis
  - Excretion of a xenobiotic/metabolite into bile canaliculus
  - Disable transport proteins/loss of villous processes prevent excretion of bilirubin

- Mixed
  - Delayed immune (hypersensitivity) reaction
  - Portal inflammation/failure of canalicular pumps allow toxic bile acids to accumulate

Patterns of Biochemical Features

<table>
<thead>
<tr>
<th></th>
<th>AK Phos</th>
<th>GGT</th>
<th>AST</th>
<th>ALT</th>
<th>Bilirubin (U)</th>
<th>Bilirubin (C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Necrosis/</td>
<td>1-2x</td>
<td>1-2x</td>
<td>10-500x</td>
<td>10-500x</td>
<td>1-10x</td>
<td>1-10x</td>
</tr>
<tr>
<td>Apoptosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steatosis</td>
<td>1-2x</td>
<td>1-2x</td>
<td>5-20x</td>
<td>5-20x</td>
<td>1-10x</td>
<td>1-10x</td>
</tr>
<tr>
<td>Microvesicular</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Macrovesicular</td>
<td>2-5x</td>
<td>2-5x</td>
<td>1-3x</td>
<td>1-3x</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Adult reference values

Patterns of Biochemical Features

<table>
<thead>
<tr>
<th></th>
<th>AK Phos</th>
<th>GGT</th>
<th>AST</th>
<th>ALT</th>
<th>Bilirubin (U)</th>
<th>Bilirubin (C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholestasis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatocana-</td>
<td>1-10x</td>
<td>3-10x</td>
<td>1-8x</td>
<td>1-8x</td>
<td>Normal</td>
<td>2-20x</td>
</tr>
<tr>
<td>licular</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Canalicular</td>
<td>1-4x</td>
<td>1-4x</td>
<td>1-4x</td>
<td>1-4x</td>
<td>Normal</td>
<td>2-20x</td>
</tr>
<tr>
<td>Mixed</td>
<td>1-10x</td>
<td>1-10x</td>
<td>10-100x</td>
<td>10-100x</td>
<td>1-10x</td>
<td>2-20x</td>
</tr>
</tbody>
</table>

*Adult reference values

Hepatotoxic Medications: SA

- Acetaminophen
- Lorazepam
- Chloral Hydrate
- Diazepam
- Codeine
- Clonidine
- Furosemide
- Spironolactone
- Propranolol
- Dipirdamole
- Warfarin
- Heparin
- Omega 3 fatty acids
- TPN
- Lipids
- Omeprazole
- Ursodiol
- Calcium carbonate
- Magnesium sulfate
- Potassium chloride
- Sodium chloride
- Tazocin
- Vancomycin
- Amphotericin B

Cholestatic Medications: SA

- Acetaminophen
- Lorazepam
- Chloral Hydrate
- Diazepam
- Codeine
- Clonidine
- Furosemide
- Spironolactone
- Propranolol
- Dipirdamole
- Warfarin
- Heparin
- Omega 3 fatty acids
- TPN
- Lipids
- Omeprazole
- Ursodiol
- Calcium carbonate
- Magnesium sulfate
- Potassium chloride
- Sodium chloride
- Tazocin
- Vancomycin
- Amphotericin B (liposomal)
Mixed cytotoxic/cholestatic
Medications: SA
- Acetaminophen
- Lorazepam
- Chloral Hydrate
- Diazepam
- Codeine
- Clonidine
- Furosemide
- Spironolactone
- Propranolol
- Dipirydamole
- Warfarin
- Heparin
- Omega 3 fatty acids
- TPN
- Lipids
- Omeprazole
- Ursodiol
- Calcium carbonate
- Magnesium sulfate
- Potassium chloride
- Sodium chloride
- Tazocin
- Vancomycin

Narrowing the field….
- Acetaminophen - HELD
- Lorazepam – PRN
- Chloral Hydrate
- Diazepam
- Codeine
- Clonidine
- Furosemide
- Spironolactone
- Propranolol - HELD
- Dipirydamole
- Warfarin
- Heparin
- Omega 3 fatty acids
- TPN
- Lipids
- Omeprazole
- Ursodiol
- Calcium carbonate
- Magnesium sulfate
- Potassium chloride
- Sodium chloride
- Tazocin
- Vancomycin
- Amphotericin B

Assessing Causality
- "There is no clinical finding that indicates DILI with certainty, including liver biopsy"1
- Can only evaluate evidence of a cause-and-effect relationship 2
  1. Temporality
  2. Strength
  3. Dose-response
  4. Reversibility
  5. Consistency
  6. Biologic plausibility
  7. Specificity
  8. Analogy

2. Fletcher RH, Fletcher SW, Wagner EH. Clinical Epidemiology; the essentials. 2nd Ed. Williams & Wilkins, 1988, USA.

Naranjo Scale
- 10-item probability scale using a weighted scoring system with nominal categories
- Validity & Reliability using 63 published ADR cases


Naranjo Scale in the ICU
- Reliability & Validity in ICU
  1. 142 suspected ADRs tested prospectively
  2. Inter-rater agreement poor
  3. Within-rater evaluation consistent
  4. Moderate correlation with expert opinion
  5. Changes proposed for specific questions

### Naranjo Scale

1. Are there previous conclusive reports on this reaction? 1/0/0
2. Did the adverse event appear after the suspected drug was given? 2/0/1
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was given? 3/0/0
4. Did the adverse reaction appear when the drug was re-administered? 4/2/0
5. Are there alternative causes that could have caused the reaction? 5/2/0
6. Did the reaction reappear when a placebo was given? 6/-1/0
7. Was the drug detected in any body fluid in toxic concentrations? 7/-1/0
8. Was the reaction more severe when the dose was increased/increasing, or less severe when the dose was decreased? 8/-1/0
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure? 9/1/0
10. Was the adverse event confirmed by objective evidence? 10/1/0

### Naranjo for Causality in Drug-Induced Liver Injury

- Not specific for hepatotoxicity
  - Chronologic criteria according to liver injury not defined
  - Idiosyncratic mechanisms not addressed
- Inferior when compared to RUCAM for selected cases


### Assessing Causality

- "Guilt by Association"
- Clinical diagnostic scale (M&V scale)
- RUCAM

### RUCAM – DILI

- Causality assessment specific to DILI
- Validated
  - using reports with positive rechallenge as external standard
  - Adult population, 49 cases/28 controls
  - Compared to CDS in 215 cases of DILI
  - RUCAM better discrimination power
- Evolving to international standard
  - Limitations identified

RUCAM - Limitations

- Not validated for pediatric patients
- Addresses multiple drugs
  - Cannot assess >1 drug at a time
- Complicated
- Arbitrary weighting system
- Limited value of select risk factors
- Use in ICU setting?
  - Some shared issues with Naranjo

Back to basics…

1. Temporality
2. Strength
3. Dose-response
4. Reversibility
5. Consistency
6. Biologic plausibility
7. Specificity
8. Analogy

Temporality

- ALT, blood
- Bilirubin-Conjugated, blood
- GGT, blood

Narrowing the field….

- Acetaminophen
- Lorazepam
- Chloral Hydrate
- Diazepam
- Codeine
- Clonidine
- Furosemide
- Spironolactone
- Propranolol
- Diprydamole
- Warfarin
- Heparin
- Omega 3 fatty acids
- TPN
- Lipids
- Omeprazole
- Ursodiol
- Calcium carbonate
- Magnesium sulfate
- Potassium chloride
- Sodium chloride
- Tazocin
- Vancomycin
- Amphotericin B
Back to basics…

1. Temporality
2. Strength
3. Dose-response
   1. Reversibility
   2. Consistency
   3. Biologic plausibility
   4. Specificity
   5. Analogy

Relevance to Practice - SA

- Biochemistry
  - ALT/AST ~5 x ULN, Bilirubin(C) ~4 x ULN
  - Tests of liver function N/A
- RUCAM
  - ~6 (probable), one question unanswered
- Weigh risks of stopping therapy
- Continue to monitor/avoid concurrent hepatotoxins

Conclusions – SA

06/01
AST=28 (0-40)
ALT=44 (0-45)
Bilirubin (c/u)= 9/0 (<17/0-2)
INR=1.3 (on warfarin)
Platelets= 102(150-400)
Albumin=38

- Changes to meds with clinical improvement
  - D/C TPN & Lipids
  - D/C heparin
  - Likely multi-factorial

Future Considerations

- Documentation of suspected DILI in the PICU/paediatric population
- Creation of a tool based on identified risks/characteristics
- Bayesian approach?
- Validation of a Causality Assessment scale
  - Consider DILI specific factors

Conclusions

- High level of suspicion for DILI
- Literature search/evaluation
- Utilize causality assessment scale if applicable
- Back to basics to assess causality
- Weigh risks to determine management
- DOCUMENT, DOCUMENT, DOCUMENT