First Pass Hepatic Metabolism

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Learning Objectives

• Describe First Pass Hepatic Metabolism

• Describe the mechanism of drugs detoxification and metabolism in the liver

• Enlist some of the commonly used hepatotoxic drugs and their toxicities
First Pass Effect

- Drugs that are absorbed via the GIT are circulated to the liver first via the hepatic portal vein
- Liver then acts as a filter
- Only part of the drug is circulated systemically
- The combination of processes is termed the ‘First Pass’ effect
Y It's called as First pass effect?
First pass metabolism:
- It means drug metabolism occurring before the drug enters the systemic circulation.
- Results is decreased bioavailability.
- Decreased therapeutic response.

Bypass First pass metabolism:
- IV route
- Sublingual route
• The four primary systems that affect the first pass effect of a drug are the enzymes of the gastrointestinal lumen, gut wall enzymes, bacterial enzymes, and hepatic enzymes.
• In drug design, drug candidates may have good drug likeness but fail on first-pass metabolism, because it is biochemically selective.
First pass Metabolism

Where does it occur?
- Liver
- Gut wall
- GIT lumen

Results in:
- Low bioavailability (low conc. of drug in blood).
- short duration of action (t ½).
- drugs with high first pass effect should not be given orally but parenterally.
First pass metabolism
Importance...???
Hepatotoxic drugs
Hepatotoxic Drugs

Introduction

- Liver plays a key role in detoxifying harmful substances.
- **Toxic hepatitis** is liver inflammation due to toxic chemicals, drugs or certain poisonous mushrooms.
- Among patients with acute liver failure, drug-induced liver injury is the most common cause.
Hepatotoxic Drugs

Classification

- Intrinsic type of hepatotoxicity
- Idiosyncratic type of hepatotoxicity
- Chronic type of hepatotoxicity
# Hepatotoxic Drugs

## Classification

<table>
<thead>
<tr>
<th></th>
<th>Intrinsic</th>
<th>Idiosyncratic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence</td>
<td>More common</td>
<td>Less common 1%</td>
</tr>
<tr>
<td>Predictability</td>
<td>Predictable</td>
<td>Unpredictable</td>
</tr>
<tr>
<td>Dose related</td>
<td>Dose dependent</td>
<td>Dose independent</td>
</tr>
<tr>
<td>Latency period</td>
<td>Short latency period</td>
<td>Variable latency period</td>
</tr>
<tr>
<td></td>
<td></td>
<td>weeks or months</td>
</tr>
<tr>
<td>Type of injury</td>
<td>Usually necrosis</td>
<td>Necrosis or apoptosis</td>
</tr>
<tr>
<td>Associated</td>
<td>Acute liver failure</td>
<td>Rash, fever, eosinophilia</td>
</tr>
<tr>
<td>Examples</td>
<td>Acetaminophen</td>
<td>Isoniazid</td>
</tr>
</tbody>
</table>
Hepatotoxic Drugs

Pathogenesis
Direct cell stress, direct mitochondria impairment and specific immune reactions

Reactive metabolites depletes GSH, covalently binding to proteins, enzymes, lipids, nucleic acid and other cell structures
# Hepatotoxic Drugs

## Patterns of drug-induced liver injury

<table>
<thead>
<tr>
<th>Type of injury:</th>
<th>Hepatocellular</th>
<th>Cholestatic</th>
<th>Mixed</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ALT</strong></td>
<td>≥ Twofold rise</td>
<td>Normal</td>
<td>≥ Twofold rise</td>
</tr>
<tr>
<td><strong>ALP</strong></td>
<td>Normal</td>
<td>≥ Twofold rise</td>
<td>≥ Twofold rise</td>
</tr>
<tr>
<td>ALT: ALP ratio</td>
<td>High, ≥5</td>
<td>Low, ≤2</td>
<td>2-5</td>
</tr>
</tbody>
</table>

**Examples**

- Acetaminophen
- Allopurinol
- Amiodarone
- HAART
- NSAID

- Anabolic steroid
- Chlorpromazine
- Clopidogrel
- Erythromycin
- Hormonal contraception

- Amitriptyline
- Enalapril
- Carbamazepine
- Sulfonamide
- Phenytoin
Hepatotoxic Drugs

Drugs causing Hepatotoxicity

1. ANTIBIOTICS
   - Amoxicillin / clavulanate
   - Trimethoprim / sulfamethoxazole
   - Fluoroquinolones
   - Macrolides
   - Nitrofurantoin
   - Minocycline

2. ANTIEPILEPTICS
   - Phenytoin
   - Carbamazepine
   - Lamotrigine
   - Valproate
Hepatotoxic Drugs

Drugs causing Hepatotoxicity

3. ANTI-TUBERCULAR:
   - Rifampicin
   - Isoniazid.

4. NSAID:
   - Acetaminophen
   - Nimesulide
   - Diclofenac

5. HYPOLIPIDEMIC DRUGS
   - STATINS
   - Niacin
   - Fibrates
Hepatotoxic Drugs

Drugs causing Hepatotoxicity

6. ANAESTHETIC AGENTS
   - Halothane
   - Chloroform
   - Isoflurane, Enflurane & Desflurane
   - Nitrous oxide.

7. ANTIRHEUMATIC DRUGS
   - Sulphasalazine
   - Gold salt
   - Azathioprine
   - Methotrexate
Hepatotoxic Drugs

Drugs causing Hepatotoxicity

8. ANTIRETROVIRAL DRUGS

- Protease inhibitors
  - Ritonavir
  - Indinavir
  - Nelfinavir

- NRTI
  - Lamivudin
  - Tenofovir
  - Zidovudine
  - Didanosine

- NNRTI
  - Nevirapine
  - Efavirenz
Hepatotoxic Drugs

Hepatitis

- Halothane
- Isoniazid
- Rifampcin
- Pyrazinamide
- Phenytoin
- Carbamazepine
- Ketoconazole
- Methyldopa
Hepatotoxic Drugs

**CHOLESTASIS**

- Erythromycin
- Rifampicin
- Amoxicillin-Clavulanic
- Nifedipine
- Verapamil
Hepatotoxic Drugs

Necrosis
Acetaminophen
Carbon tetrachloride
Yellow phosphorus
HEPATOTOXIC DRUGS

CLINICAL MANIFESTATIONS

**Acute presentations of drug-induced liver injury (DILI)** include:
- mild asymptomatic liver test abnormalities
- cholestasis with pruritus
- an acute illness with jaundice that resembles viral hepatitis
- acute liver failure

**Chronic liver injury** can resemble other causes of chronic liver disease, such as:
- autoimmune hepatitis
- primary biliary cirrhosis
- sclerosing cholangitis
- alcoholic liver disease.

• In some patients, chronic injury secondary to DILI progresses to cirrhosis.
Treatment:

- **No specific treatment** exists for most kinds of toxic hepatitis.
- For most other cases of drug-induced toxic hepatitis, **stopping the medication** is the only treatment.

Other treatments include:

- **Supportive therapy**. People with severe symptoms are likely to receive supportive therapy in the hospital, including intravenous fluids and medication to relieve nausea and vomiting.
- **Liver transplant**. When liver function is severely impaired, a liver transplant may be the only option for some people.
Hepatotoxic Drugs

Treatment:

- **No specific treatment** exists for most kinds of toxic hepatitis
- For most other cases of drug-induced toxic hepatitis, **stopping the medication** is the only treatment.
- **Supportive therapy** - People with severe symptoms are likely to receive supportive therapy in the hospital, including intravenous fluids and medication to relieve nausea and vomiting.
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Hepatotoxic Drugs

Conclusion

• Drug-induced hepatotoxicity is a significant clinical problem.

• Current preclinical test systems for hepatotoxicity are inadequate, reflecting our limited understanding of mechanisms of drug toxicity, particularly the “hypersensitivity” or “idiosyncratic” types of reactions.

• The main challenge is to be able to detect drug induced mitochondrial dysfunction during preclinical studies.
THANK YOU