Hepatotoxic Drugs

objectives

- Define the role of liver in drug detoxification
- Discuss the types (patterns) of hepatotoxicity
- Classify hepatotoxins
- Explain how a drug can inflict hepatotoxicity
- State the pathological consequences of hepatic injury
- Contrast the various clinical presentation of hepatotoxicity
- Enlist the possible treatment

extra information and further explanation

important

doctors notes

Drugs names

Mnemonics

Kindly check the editing file before studying this document
Regulation, synthesis & secretion

utilization of glucose, lipids & proteins + bile for digesting fats.

Storage

Glucose (as glycogen), fat soluble vitamins (A, D, E & K) & minerals.

Purification, transformation & clearance

of endogenous (steroid hormones, cholesterol, FA, & proteins..) & exogenous (drugs, toxins, herbs...etc) chemicals.

• Has multiple functions (>5000)

Can be categorized into:

Pharmacological

Human body identifies almost all drugs as foreign substances i.e. XENOBIOTIC

Has to get rid of them

"METABOLIC CLEARING HOUSE"
• Liver subjects drugs to chemical transformation (metabolism) to become inactive and easily excreted “convert drugs from lipophilic $\rightarrow$ Hydrophilic to excrete in urine”

• Since most drugs are lipophilic they’re changed into hydrophilic water soluble products for elimination through the bile or urine.

Such metabolic transformation usually occur in 2 phases:

**Phase 1 reactions**

- Oxidation, Reduction, Hydrolysis, Hydration Catalyzed by CYT P-450

**Phase 2 reactions**

- Conjugation with a moiety (acetate, a.a., glutathione, glucuronic a., sulfate)

- Yields intermediates $\rightarrow$ polar, transient, usually highly reactive $\rightarrow$ far more toxic than parent substrates $\rightarrow$ may result in liver injury $\rightarrow$ Drug-Induced Liver Injury (DILI)

- Yields products of increased solubility
  - If of high molecular weight $\rightarrow$ excreted in bile.
  - If of low molecular weight $\rightarrow$ to blood $\rightarrow$ excreted in urine.
**Hepatotoxic drugs**

- Hepatotoxic drugs are the leading cause of ADRs.

Hepatotoxic drugs → drug induced liver injury (Inflammation → Apoptosis → Necrosis).

Injury / damage of the liver is caused by exposure to a drug → Inflicts varying impairment in liver functions → Manifests clinically a long range → hepatitis → failure

**Why the liver is the major site of ADRs?**

- It is the first organ to come in contact with the drug after absorption from the GIT.
- Being the metabolic clearing house of the body → it expresses the highest levels of drug metabolizing enzymes that converts some drugs (PROTOXINS) into intermediate (TOXINS) before being conjugated for elimination.

Drug (Pro-toxin) → Toxin → Injury.

Paracetamol → CYT P450 → NABQI lead to centrilobular liver necrosis.

(NAPBQI) : N-acetyl-p-benzoquinone imine.

**Can any drug cause liver-related ADRs?**

- Not all drugs do so
- Drugs that can cause ADRs in the liver (hepatotoxicity) are called → HEPATOTOXIN.

**Toxicity potential of the drug**

- Chemical composition of the drug itself.
- Nature of its reactive metabolite.
- Conjugation reactions linked to it & their availability.
- Mitochondrial effects of the drug.
- Drug formulation (Long-acting drugs).
If the toxicity of HEPATOTOXIN is inflected by:

**Supertherapeutic / Cumulative dose of the drug**
- **INTRINSIC** Hepatotoxin
  - **Type** of the hepatotoxicity inflected:
    - **DIRECT** hepatotoxicity
  - **Belong to** type A (dose dependent) ADRs
  - Predictable/ Direct

- **IDIOSYNCRATIC** Hepatotoxin
  - **Type** of the hepatotoxicity inflected: Due to hypersensitivity
  - **INDIRECT** hepatotoxicity
  - **Belong to** type B (dose independent) ADRs
  - Unpredictable/Bizzar/Idiosyncratic

**DIRECT increased dose dependent Hepatotoxicity**
- Acetaminophen
- Salicylates
- Statins
- Amiodarone
- Oral Contraceptives
- Methotrexate
- Alcohol

**DIRECT cumulative Hepatotoxicity**
- Increased dose
- Normal dose of the drug

**Type B dose dependent is divided into:**

<table>
<thead>
<tr>
<th>Immunoallergic idiosyncratic hepatotoxicity</th>
<th>Metabolic idiosyncratic hepatotoxicity</th>
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<tbody>
<tr>
<td>A drug or its metabolite binds to hepatic membranes or proteins → act as hapten to induce a variety of immune reactions.</td>
<td>The metabolite of the offending drug interferes with hepatic metabolism as that of bilirubin or protein synthesis...etc</td>
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</tbody>
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**Drugs causing Viral Hepatitis-like pattern:**
- Isoniazid anti TB
- Phenotoin anti epileptic
- Methyldopa

**Drugs that interfere with bilirubin metabolism:**
- Erythromycin
- Rifampicin

**Drugs that interfere with protein synthesis:**
- Corticosteroids
- Tetracycline

**Drugs causing Inflammatory cholestasis:**
- Chlorpromazine
- Chlorpropamide
- Erythromycin

**Drugs that cause these types of hepatotoxicity**
e.g. when we give oral anti-coagulant we predict that bleeding could be one of ADRs

e.g. when we give antibiotic and the pt. has sudden reaction to it → not predicted
Drug or its reactive metabolites can form **covalent bonds** with target molecules or alter the target molecule by **non-covalent** interactions or both.

### Covalent interactions:
- **change in molecule itself**
- A type of chemical bond involving the sharing of electrons between atoms in a molecule (strong)
- It is adduct formation between the metabolite of the drug & cellular macromolecules.

- If covalent binding to protein → immunogenic reaction
- If binding to DNA → carcinogenesis

### Non-Covalent interactions:
- **change in function**
- - Lipid peroxidation → generation of cytotoxic oxygen radicals.
- - Impairment of mitochondrial respiration.
- - Depletion of GSH reactions → 'oxidative stress'
- - Modification of sulfhydryl groups → impair Ca\(^{2+}\) homostasis
- - Protein synthesis inhibition
  ...etc

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**Hepatotoxins cause liver disease**

Most Hepatotoxins cause liver disease only in certain persons depending on:

- **Environmental factors:**
  - Race, Age, Sex, Nutritional status, Concomitant habits, drugs, diseases
- **Host genetic makeup:**
  - Metabolizing Enzymes, Detoxifying System, Drug Transport

**Incidence of hepatotoxicity depends on:**

- Toxicity potential
- Host genetic makeup
- Environmental Host factors

Those factors lead to: **Drug induced hepatotoxicity**
Drugs produce about 10% of all cases of hepatitis in young adults and 40% of cases in patients older than 50 years.

**Categories of people who are exposed to Hepatotoxins:**

- **Tolerators**
  - No injury

- **Adaptors**
  - Mild transient injury but adapt

- **Susceptibles**
  - Develop overt symptoms depending on existing predisposing factors

- **In threat**
  - DIHI accelerates beyond initial targets due to loss of synthetic & clearance function of hepatocyte with recruitment of inflammatory cells provoke apoptotic & necrotic signals

**Incidence of DIHI**

- *short* (hrs/dys), *intermediate* (1-8ws), *long* (1-12ms)

- **In Direct dose-dependent Hepatotoxicity** → the Latency period is **SHORT** as it occurs after a threshold of toxicity is reached → acetaminophen

- **In Direct cumulative or In Indirect immunoallergic Idiosyncratic Hepatotoxicity** → the Latency period is **INTERMEDIATE**, but may continue to evoke even after drug

- No universal histo-pathological pattern of DIHI exist.
  - The commonest are: **Hepatocellular necrosis**, **Cholestasis**, **Steatosis**.
  - More than one type of injury may occur in the same patient and Any one agent may produce different types of injury in different patients

**Clinical pattern:** Will be explained in the next slide
**Clinical patterns**

The clinical presentation could be of variable intensity ranging from asymptomatic ↑ of liver enzymes to Fulminant hepatic failure.

<table>
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<th>ASYMPTOMATIC</th>
<th>SYMPTOMATIC MANIFESTATIONS</th>
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<td><strong>increase In aminotransf-erases</strong></td>
<td><strong>injury targets hepatocytes</strong></td>
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- **Hepatocellular**
  - If injury targets **biliary system (canalicular or ductal)** (CHOLESTASIS)
  - **Examples**
    - Hepalin
    - Statins
    - Sulfonamides
    - Sulfonylureas

- **Symptoms**: develop rapid onset of malaise, severe anorexia (loss of appetite) and jaundice, Flu-like symptoms, muscle aches, weakness, GIT symptoms, diarrhea, urine discolored,

  - Increase (3 fold) in alanine aminotransferases (**ALT**).
  - Normal level of **ALP**.

- **Examples**: Acetaminophen, NSAIDs, Isoniazid, Amiodarone

| **If injury targets both hepatocytes & biliary system (MIXED TYPE)** |

- **Symptoms**: develop jaundice + severe pruritis predominate, dark urine, rash, stool may be light, hyperbilirubinemia

- **Examples**: Phenobarbital, Carbamazepine, Sulfonamides, ACE Inhibitors

- **ALT**: increase 3 folds

- **ALP**: increase 2 folds
1st step: Immediate withdrawal of any suspected drug.

No specific treatment, largely **symptomatic & supportive**:

**Symptomatic:**
- If a severe allergic reaction is observed  
  *(Corticosteroids)*
- If pruritus → enhance bile acid excretion  
  *(Cholestyramine)*
- If cholestatic liver injury  
  *Ursodeoxycholic acid (Ursodiol)*
- If coagulopathy or encephalopathy develop → treat accordingly

**Supportive:**
High carbohydrate, moderate protein and fat diet adequate in calories

**Specific antidotes:**
- For Acetaminophen toxicity → **N-acetylcysteine**
- For Valproate toxicity → **L-carnitine**

For Drug induced Fulminant Hepatic failure

↓

Emergency liver transplantation
Case 1

A long standing rheumatoid arthritic patient developed TB 2 months ago. Today she was received in the ER complaining of yellowish discoloration, severe anorexia, vomiting, and flu like manifestations since two days. She is very weak and looks toxic. Her drug history reveals that she has been 4 months ago on cyclosporine to control the arthritic exacerbations. A month ago, she was put on isoniazid when she developed TB and multivitamins because she is weak. Currently she is given domperidone for the emesis. Lab results reveals severe elevation in ALT but no elevation on ALP.

Q1: Which one of the following drugs is the likely cause of her symptoms?
A. Cyclosporine
B. Multivitamins
C. Isoniazid
D. Domperidone

Q2: Which type of Hepatotoxin is considered?
Immunoallergic  Idiosyncrotic

Q3: What is the likely hepatotoxic pattern inflicted by the drug?
Hepatocellular / Hepatitis-like pattern

Case 2

A hypercholesterolemic patient was received in the ER complaining of yellowish discoloration of the skin, change in the color of the urine & stools, and severe itching. He has been receiving statins for the long time for the hypercholestremia. 3 months ago he was diagnosed as being diabetic and hypertensive and since then he is receiving chlorpropamide for the diabetes and nadolol for the hypertension. The last couple of days he has a flu for which he was given acetaminophen for muscle aches and nasal drops for his nasal stuffiness. Lab investigation shows severe elevation of ALP and no significant elevation in ALT.

Q1: Which one of the following drugs is the likely cause of his symptoms?
A. Nadolol
B. Chlorpropamide
C. Acetaminophen
D. Statins

Q2: Which type of Hepatotoxin is considered?
Immunoallergic  Idiosyncrotic

Q3: What is the likely hepatotoxic pattern inflicted by the drug?
Cholestasis / Inflammatory cholestasis
قادة فريق علم الأدوية:
- جومانا القحطاني
- اللولو الصليهم
- فارس النفيضة

الشكر موصول لأعضاء الفريق المتميزين:
- روآن القحطاني
- ليلي المذكور
- أنوار العجمي
- دعاء وليد

References :
1- 436 Prof. Yieldez  slides and notes
2- male’s notes