MED438

pharmacology
Team 438

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Hepatotoxic Drugs

Objectives:

By the end of the lecture , you should know:

- 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

★ **The Drugs mentioned in the lecture are VERY important, know them and to which category they belong.**

Color index:

Black : Main content
Red : Important
Blue: Males' slides only
Purple: Females' slides only
Grey: Extra info or explanation
Green : Dr. notes

Editing File

Liver Functions:

Liver has multiple functions (>5000) ➔ can be categorized into:

Utilization of glucose, lipids & proteins + bile for digesting fats	Glucose (as glycogen), fat soluble vitamins (A,D,E,K) & minerals	Of endogenous (steroid hormones, cholesterol, FA & proteins) & exogenous (drugs, toxins, herbs) chemicals
Regulation, synthesis, secretion	**Storage**	**Purification, transformation & clearance**

In case of the drugs:

Human body identifies almost all drugs as foreign substances i.e. Xenobiotic → Has to get rid of them → thus , liver considered as **Metabolic clearance housing**

Metabolism of Drugs in the Liver

- Liver subjects drugs to chemical transformation (metabolism) to become **inactive and easily excreted**
- Since most drugs are lipophilic they're changed into hydrophilic water soluble to be suitable for elimination through the bile or urine.
  - **Such metabolic transformation usually occur in 2 phases:**

Phase 1 Reaction	VS	Phase 2 Reaction
Oxidation, Reduction, Hydrolysis, Hydration Catalyzed by **CYT P-450**		Conjugation with a moiety (acetate, a.a., glutathione, Glucuronic a., sulfate)
Yields **intermediates**→ polar, transient, usually highly reactive→ far **more toxic** than parent substrates→ may result in liver injury [**Drug-Induced Liver Injury** (DILI)]		Yields products of increased solubility: • If of high molecular weight → excreted in bile. • If of low molecular weight→ to blood→ excreted in urine.

Hepatotoxic Drugs

Hepatotoxic drugs: are drugs that induced liver injury.

1. Hepatotoxicity is the leading cause of ADRs.
2. **Injury / damage of the liver** (Inflammation→Apoptosis→Necrosis) is Caused by: exposure to a drug→ Inflict varying impairment in liver functions → Manifests clinically a long range → hepatitis → failure

Why the Liver is the major site of ADRs?

1. It is the **first** organ to come in contact with the drug after absorption from the GIT

2. 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]

Example:

Paracetamol→ CYT P450 → **NABQI** → centrilobular liver injury

(**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)

Types of drug-induced hepatotoxic

1 Intrinsic hepatotoxin

Causes Direct hepatotoxicity.

- Inflicted by:
  1. Super-therapeutic (increased) dose
  2. Cumulative dose [1]
- belong to **type A** ADRS :
  - **predictable** /direct.
  - **Dose-dependent** hepatotoxicity

2 Idiosyncratic hepatotoxin

Causes Indirect hepatotoxicity

- Inflicted by: Normal dose.
- Belong to **type B** ADRS:
  - **bizarre / unpredictable / idiosyncratic** .
  - **Dose-Independent** hepatotoxicity.

1) Total dose that results from repeated exposure to a drug e.g prolonged use of oral contraceptives can lead to hepatotoxicity

Drugs that causes Intrinsic hepatotoxin

Increased Dose	Cumulative Dose	Both
• Acetaminophen • Salicylates • Statins	• Amiodarone • Oral contraceptive	• Methotrexate • Alcohol

Drugs that causes Idiosyncratic hepatotoxin

Divided into:

Hypersensitivity or Immunologic reactions:
A drug or its metabolite binds to hepatic membranes or proteins which act as **hapten**[1] to induce a variety of immune reactions.

Metabolic-idiosyncratic reactions:
The metabolite of the offending drug **interferes** with hepatic metabolism as that of bilirubin or protein synthesis...etc

Immunologic-idiosyncratic Hepatotoxicity		Metabolic-idiosyncratic Hepatotoxicity	
Inflammatory cholestasis	Viral hepatitis-like pattern	Interfere with bilirubin metabolism	Interfere with protein synthesis
• Erythromycin • Chlorpropamide • Chlorpromazine	• Isoniazid • Phenytoin • Methyldopa	• Erythromycin • Rifampicin	• Corticosteroid • Tetracycline

"Note that not all drugs fall neatly into one of these categories, and overlapping mechanisms may occur with some drugs"

How can a drug induces hepatotoxicity?

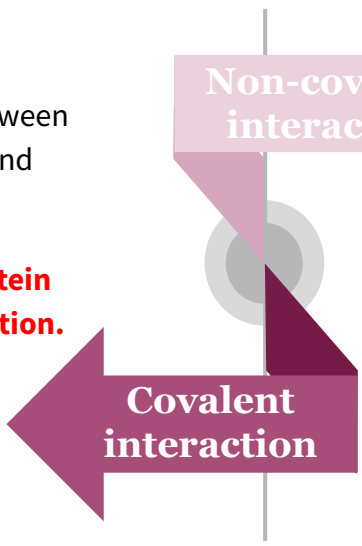
Drug or its reactive metabolites can form **covalent bonds** with target molecules or **alter the target molecule** by **non-covalent interactions** or both.

1- **Stronger**

2- It is adduct formation between the metabolite of the drug and cellular macromolecules

3- If covalent binding **to protein** leads to **immunogenic reaction.**

4- If binding to **DNA** become **carcinogenesis**.



1- Weaker

2- Lipid peroxidation → generation of cytotoxic oxygen radicals.

3- Impairment of mitochondrial Respiration.

4- Depletion of GSH → reactions leads to oxidative stress.

5- Modification of sulfhydryl groups → impair Ca2+ homeostasis.

6- Protein synthesis inhibition.

1.a small molecule which, when combined with a larger carrier such as a protein, can elicit the production of antibodies which bind specifically to it .

Do hepatotoxins cause liver disease in all people?

Most hepatotoxins cause liver disease **only in certain persons** depending on:

Environmental host Factors


Age


Disease


Race


Sex


Nutritional status


Concomitant habits


Drugs

Host genetic makeup

1. Metabolizing enzymes
2. Detoxifying system
3. Drug transport

Drug-Induced Hepatic Injury (DIHI)

Is DIHI common?

Incidence of DIHI:

- Drugs produce about 10% of all cases of hepatitis in young adults.
- 40% of cases in patients older than 50 years.

Are certain persons or population more susceptible ?

Upon exposure to hepatotoxins people are categorized as:

Tolerators	No Injuries
Adaptors	Mild transient injury but adapt
Susceptibles	Develop overt symptoms depending on existing predisposing factors
In Threat	DILI accelerates beyond initial targets due to loss of synthetic & clearance function of hepatocyte with recruitment of inflammatory cells provoke apoptotic & necrotic signals

[1. Toxicity potential of the drug 2. Environmental host factors 3. Host genetic makeup]

Those factors determine the patient's response to hepatotoxins

What are the presenting manifestations?

Individual drugs tend to have characteristic signature composed of:

1. A particular latency period
2. A clinical pattern
3. A particular pathological finding

Latency Period

Short (hrs\days)	Intermediate (1-8ws)	Long (1-12ms)
Direct dose dependent hepatotoxicity: Latency period is **short** as it occurs after a threshold of toxicity is reached. E.g acetaminophen (toxic dose)	**Direct cumulative or In Indirect Immunoallergic Idiosyncratic Hepatotoxicity:** Latency period is **intermediate**, but may continue to evoke even after drug withdrawal. E.g -amiodarone(cumulative) -phenytoin, isoniazid (idiosyncratic)	**In indirect metabolic idiosyncratic hepatotoxicity:** latency period is **usually long**, unpredictable and most problematic E.g tetracycline, oral contraceptives

Clinical Pattern

The clinical presentation could be of variable intensity, ranging from asymptomatic slightly increased liver enzymes to fulminant hepatic failure.

A) Some drugs just induce Asymptomatic increase in the enzymes (Aminotransferase)

Phenytoin → Statins → Sulfonamides → Sulfonylureas

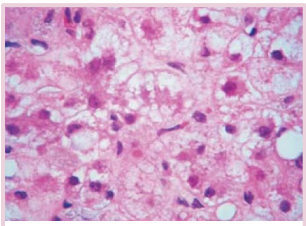
B) Other drugs induce symptomatic manifestations

Some Patterns of **symptomatic** drug-induced liver disease:

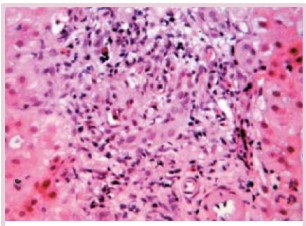
Hepatic Injury	Hepatocellular	Cholestatic	Mixed
How They Develop	If injury targets hepatocytes → apoptosis or necrosis → HEPATITIS (cytotoxic) develops → rapid onset of malaise, severe anorexia and jaundice + ↑ in alanine aminotransferases (ALT)	If injury targets biliary system (canalicular or ductal) → CHOLESTASIS develop → jaundice +\- severe pruritus predominate → ↑ in alkaline phosphatase (ALP) +\- hyperbilirubinemia.	if injury targets both hepatocytes & biliary system→ MIXED TYPE.
Symptoms	Flu-like, malaise, m. aches weakness, loss of appetite, GIT symptoms, diarrhea, jaundice, urine discolored.	Yellowish discoloration of skin, dark urine, rash, pruritus, stool may be light	Symptoms of both types of injury (Hepatocellular and Cholestatic) are present with elevation of both enzymes
ALT	≥ 3 fold rise	Normal or slight	≥ 3 fold rise
ALP	Normal	≥ 2 fold rise	≥ 2 fold rise
E.g	1. Acetaminophen 2. NSAIDs 3. Isoniazid 4. Amiodarone	1. Chlorpropamide 2. Erythromycin 3. Rifamycin 4. Oral contraceptives	1. Phenytoin 2. Carbamazepine 3. Sulfonamides 4. ACE Inhibitors

Histopathological Patterns

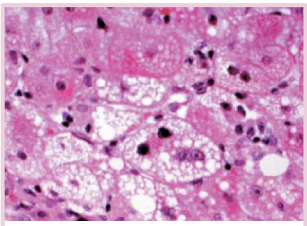
- No universal histopathological pattern of DIHI exist; the commonest are:
  a. Hepatocellular necrosis b. Cholestasis c. Steatosis
- More than one type of injury may occur in the same patient
- Any one agent may produce different types of injury in different patient



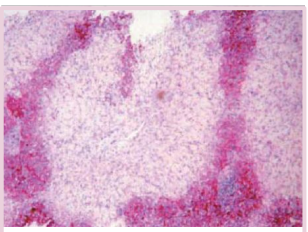
Ballooning & degeneration of hepatocyte



Cholestatic injury with damaged bile duct



Fatty accumulation



Centrilobular & Midzonal necrosis

Lines of Treatment

Immediate withdrawal	• Of any suspected drug	
No specific treatment	**Symptomatic:** ★ **Corticosteroids** for **severe allergic reaction** is observed ★ **Cholestyramine** for **Pruritus** to enhance bile acid secretion ★ **ursodeoxycholic acid (Ursodiol)** for **Cholestatic** liver injury • Coagulopathy or encephalopathy develop (treat accordingly)	**Supportive:** • High carbohydrate • Moderate protein diet Adequate in calories
Specific antidotes	★ **N-acetylcysteine** for **acetaminophen toxicity** ★ **L-carnitine** for **valproate toxicity**	
Emergency liver transplantation	• For any drug induced fulminant hepatic failure	

Cases from Dr Slides

A long standing rheumatoid arthritic patient developed **tuberculosis** 2 month ago. Today she was received in E.R complaining of yellowish discoloration of skin**, 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 month ago on cyclosporine to control the arthritis exacerbations. A month ago, she was put on **isoniazid** when she developed T.B. and multivitamins because she is weak. Currently she is given domperidone for the emesis. Lab results reveals **severe elevation in ALT but no elevation in ALP.**

Q1) Which of the following drugs is the most likely cause of her symptoms?

a) Cyclosporine b) Multivitamins c) isoniazid d) Domperidone

Q2) Which type of hepatotoxin is it considered?

Q3) What is the likely hepatotoxic pattern inflicted by the drug?

Q4) Which drug can be used for the treatment of her condition?

Q1) C Q2)Immunoallergic Idiosyncratic (Viral Hepatitis-like pattern) Q3) Hepatocellular Q4) Corticosteroids

A hypercholesterolemic patient was received in E.R complaining of **yellowish discoloration of skin**, **change in color of urine & stools**, and severe itching
He has been receiving **statins** for the long time for the hypercholesterolemia. Three month 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 had a flue; for which he was given **acetaminophen** for muscle aches and nasal drops for his nasal stuffiness. Lab investigations shows **severe elevation in ALP and no significant elevation in ALT**.

Q1) Which of the following drugs is the most likely cause of her symptoms?

a) Nadolol b) Chlorpropamide c) Acetaminophen d) Statins

Q2) Which type of hepatotoxin is it considered?

Q3) What is the likely hepatotoxic pattern inflicted by the drug?

Q4) Which drug can be used for the treatment of her condition?

Q1) B Q2)Immunoallergic Idiosyncratic (Inflammatory cholestasis) Q3)Cholestasis Q4) Ursodiol \ Cholestyramine

Quiz

MCQ

1- Hepatitis is an injury in:

A- Biliary system B- Hepatocytes C- A&B

2- Which of the following antitubercular drug interferes with bilirubin metabolism? :

A- Isoniazid B- Rifampicin C- Ethambutol

3- ALT (alanine aminotransferase) and ALP (Alkaline Phosphatase) both will be increased in :

A- Cholestatic B- Hepatocellular C- Mixed type

4- Drugs that cause intrinsic hepatotoxin are?

A- Indirect Hepatotoxic B- Belong to TYPE B ADRs C- Dose dependent

5- If a covalent interaction happened between the metabolite of the drug and the proteins which of the following will happen?

A- Immunogenic reaction B- Carcinogenesis C- Oxidative stress

SAQ

Q1-A 63-year-old man presents to the emergency department with altered mental status after ingesting an entire bottle of acetaminophen. The patient's heart rate is 120 beats/minute, blood pressure is 100/58 mm Hg, and respiration rate is 28/minute. His aspartate aminotransferase and alanine aminotransferase are 4,128 IU and 3,978 IU, respectively. What is the most appropriate treatment for this patient?

2-3.A patient came to the clinic with a history of pruritus, yellowish discoloration of the skin and dark urine.

Q2-What is the type of hepatic injury in this case?

Q3-What is the best drug to be given in this case?

Q4-A patient took an increased dose of drug A, after one hour he developed anorexia and muscle aches. what is drug A?

Q5- A patient use phenytoin as a treatment for epilepsy, he takes his medication regularly in the therapeutic dose, eventually he develop hepatitis. What is the type of ADRs for in this condition?

Answers:

MCQ

Q1	B
Q2	B
Q3	C
Q4	C
Q5	A

SAQ

Q1	N-Acetylcysteine
Q2	Cholestatic hepatic injury
Q3	Ursodiol\Cholestyramine
Q4	Acetaminophen (check slide 6 and 4)
Q5	Type B: bizarre / unpredictable / idiosyncratic

Share with us your ideas !

Good Luck , Future Doctors!

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