Hepatotoxic drugs

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- Main text
- Male slide
- Female slide
- Important
- Dr, notes
- Extra info

EDITING FILE

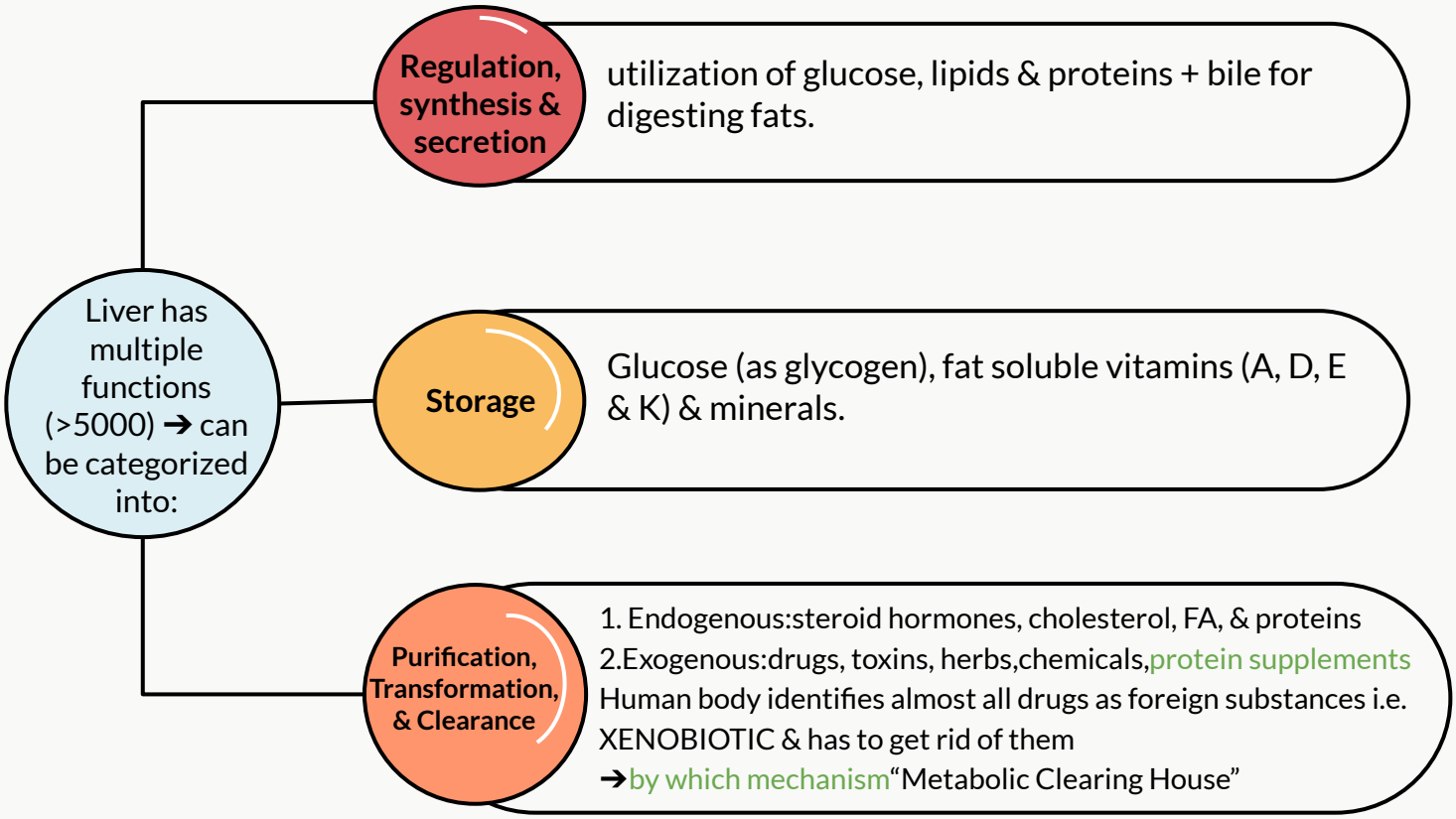
Objectives

- 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 varied clinical presentation of hepatotoxicity
- Enlist the possible treatment

Summary

Dr. Fouda (Drug metabolism)

Liver functions



Metabolism Of Drug 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 products by conjugation to be suitable for elimination through the bile or urine
- Such metabolic transformation usually occur in 2 phases:

Phase	Phase 1	Phase 2
Reaction	Catalyzed by CYP450 : • Oxidation • Reduction • Hydrolysis • Hydration	Conjugation with a moiety: • Acetate • Amino acids • Glutathione • Glucuronic acid • Sulfate
Products	•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:** • High molecular weight →excreted in bile • Low molecular weight → to blood → excreted in urine

Hepatotoxic Drugs

Definition

Hepatotoxic drugs Are (drugs induce liver injury):

- Injury/damage of the liver Is caused by exposure to a drug → Inflict varying impairment in liver functions → Manifests clinically **a long range** → leading to (hepatitis=inflammation → Apoptosis → Necrosis) → failure
- Hepatotoxicity is the leading cause of ADRs

Why is the liver 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 convert some drugs (PROTOXINS) into intermediate (TOXINS) before being conjugated for elimination second stage

→ Drug Pro-toxin → Toxin→ Injury
Ex: Paracetamol (**protoxin**) → CYT P450(phase 1)→ NABQI **toxin**→ centrilobular 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 are :**

- 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)

Do hepatotoxins cause liver injury in all people?

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

Environmental host factors:
Age-Sex-Race
-Diseases-Nutritional Status
Concomitant Habits-Drugs

Host Genetic Makeup:
Metabolizing enzymes
Detoxifying System
Drug Transport

The Alien from the Pathology took a trip to Pharmacology just to ask you this :
What antihypertensive drug class can cause hepatotoxicity?

A. Angiotensin-converting enzyme (ACE) inhibitors
B. Beta-adrenergic blocking agents
C. Angiotensin II receptor blockers (ARBs)
D. Calcium channel blockers

Answer: A , CVS BLOCK

Which enzyme is the most specific when evaluating for liver damage?

A. Aspartate aminotransferase (AST)
B. Alkaline phosphatase
C. Alanine transaminase (ALT)
D. Blood urea nitrogen (BUN)

Answer: C , Biochemistry Lecture

Is DIHI -Drug induced hepatic injury common?

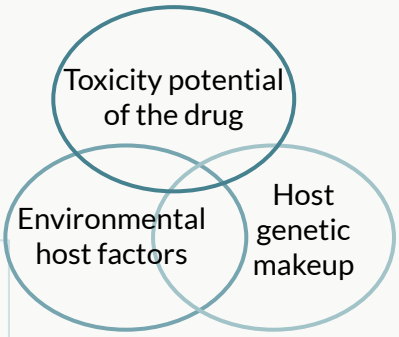
Incidence of DIHI:

- Drugs produce about 10% of all cases of hepatitis in young adults.
- 40% of cases in patients older than 50 years, because metabolism tends to slow down with age

Are certain persons or population more susceptible ?

Upon exposure to hepatotoxins people are categorized as:

Tolerators	Adaptors	Susceptibles	In threat
No Injuries Even if they took the hepatotoxin they won't get injured	Mild transient injury but adapt	Develop overt symptoms depending on existing predisposing factors	DIHI accelerates beyond initial targets due to loss of synthetic & clearance function of hepatocyte with recruitment of inflammatory cells provoke apoptotic & necrotic signals



Types of drug induced hepatotoxic ADRs

Intrinsic hepatotoxin

In this type we know we predict the ADRs

Causes Direct hepatotoxicity.

- Inflicted by:

1. 1. Super-therapeutic (increased) dose.
2. Cumulative dose (taken chronically)

- **Belong to type A ADRs:**

1. Predictable/direct
2. Dose-Dependant hepatotoxicity

Idiosyncratic hepatotoxin

Here we gave the patient the normal dose but he developed UNPREDICTABLE ADRs

Causes Indirect hepatotoxicity.

- Inflicted by: Normal dose.
- Belong to type B ADRs:

1. Bizarre/Unpredictable /idiosyncratic (unusual).
2. Dose-Independent hepatotoxicity.

1- Intrinsic hepatotoxin (Type A)

Important

Drugs that causes Intrinsic hepatotoxin (Type A)

Increased Dose	Cumulative Dose Drugs that people Used chronically	Both
• Acetaminophen paracetamol • Salicylates Aspirin • Statins	• Amiodarone • Oral contraceptive	• Methotrexate • Alcohol

2- Idiosyncratic hepatotoxin (Type B)

Divided into

Hypersensitivity or Immunologic reactions

A drug or its metabolite binds to hepatic membranes or proteins which act as **hapten** to induce a variety of immune reactions.

Hepten: small molecule that initiate immune response only when attached to a large molecule such as proteins

Metabolic-idiosyncratic reactions

The metabolite of the offending drug interferes with hepatic metabolism as that of bilirubin or protein synthesis...etc

Idiosyncratic hepatotoxin (Type B)

Immunologic-idiosyncratic Hepatotoxicity		Metabolic-idiosyncratic Hepatotoxicity	
Inflammatory cholestasis	**Viral hepatitis Like pattern**	**Interfere with bilirubin metabolism**	**Interfere with protein synthesis**
• Chlorpromazine Antipsychotic • Chlorpropamide Antihyperglycemic agent • Erythromycin	• 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"

What are the signs and symptoms of hepatotoxicity? Select all that apply.

A. Loss of appetite
B. Yellowing of the skin or eyes
C. Night sweats
D. Dark-colored urine
E. Pain in the upper abdomen

Answer: A-B-D-E

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.

Non-covalent interaction	Covalent interaction
1-Weaker 2- Lipid peroxidation → generation of cytotoxic oxygen radicals. 3- Impairment of mitochondrial Respiration. 4- Depletion of GSH reactions (reduced glutathione) → reactions leads to oxidative stress. 5- Modification of sulfhydryl groups → impair Ca2+ homeostasis. 6- Protein synthesis inhibition.	1- Stronger 2- Adduct (Protein-drug) formation between the metabolite of the drug and cellular macromolecules 3- If covalent binding to protein → immunogenic reaction. 4- If binding to DNA → carcinogenesis

Presenting manifestations

Individual drugs tend to have characteristic signature composed of:
1- A Particular latency period
2- Clinical pattern
3- A particular pathological finding

1. Latency period

Latency period	Type of hepatotoxicity	Example
Short (Hours to days) -Latency period is short as it occurs after a threshold of toxicity is reached	Direct-Dose dependent	Acetaminophen(toxic does)
Intermediate (1-8 weeks) -Latency period is intermediate, but may continue to evoke even after drug withdrawal.	Direct Cumulative	Amiodarone
	Indirect -Immunoallergic Idiosyncratic	Phenytoin isoniazid
Long (1-12 months) -Latency period is usually long unpredictable and most problematic	Indirect -metabolic Idiosyncratic	Tetracycline Oral contraceptive

Presenting manifestations Cont..

2. Clinical patterns

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

A- Symptomatic manifestations

Hepatic injury	Hepatocellular	Cholestatic	Mixed
How they develop	If injury targets hepatocytes → apoptosis or necrosis → Hepatitis (cytotoxic) ●jaundice ●rapid onset of malaise ●severe anorexia ●↑ alanine aminotransferases (ALT)	If injury targets biliary system (canalicular or ductal) → Cholestasis ● jaundice ●+\- severe pruritus predominant ●↑alkaline phosphatase ALP ●+\- hyperbilirubinemia.	if injury targets both hepatocytes & biliary system→ Mixed Type Mixed symptoms
Symptoms	Flu-like, malaise, muscle 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 [2]) 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
Example	• NSAIDs • Isoniazid • Amiodarone • Acetaminophen	• Chlorpropamide • Erythromycin • Rifamycin • Oral contraceptives	• Phenytoin • Carbamazepine • Sulfonamides • ACE inhibitor

B- Asymptomatic manifestations

Asymptomatic increase in the enzymes -aminotransferase

Examples	• Phenytoin • Sulfonamides • Statins • Sulfonylurea

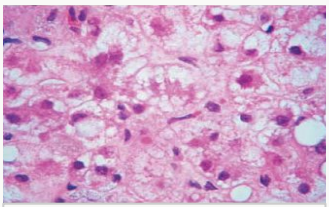
Presenting manifestations Cont..

3. Histopathological Patterns

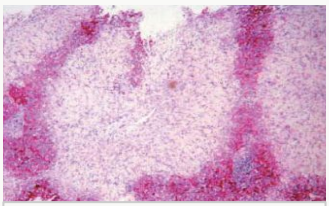
No universal histopathological pattern of DIHI exist; the commonest are
a. Hepatocellular necrosis b. Cholestasis c. Steatosis

More than one type of injury may occur in the same patient

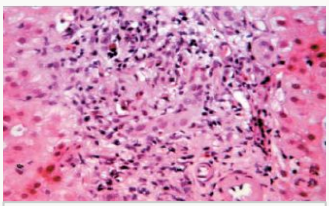
Any one agent may produce different types of injury in different patient



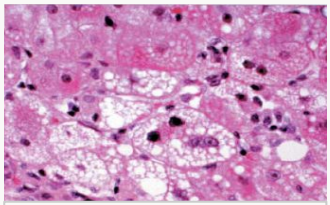
Ballooning& degeneration of hepatocyte



Centrilobular & midzonal necrosis



Cholistatic injury with damaged bile duct



Fat accumulation
Steatosis

Lines of treatment

1. Immediate withdrawal of any suspected drug - first thing to do
2. No specific treatment (largely symptomatic & supportive)
3. Specific antidotes
4. Emergency liver transplantation

No specific treatment

symptomatic	Supportive
• Corticosteroids for severe allergic reaction • Cholestyramine for Pruritus to enhance bile acid secretion • Ursodeoxycholic acid (ursodiol) for cholestatic liver injury. • Coagulopathy or encephalopathy develop (treat accordingly)	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 the 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 one of the following drugs is the likely cause of her symptoms?
A.Cyclosporine b. Multivitamins C.Isoniazid d. Domperidone
A1) C

Q2) Which type of hepatotoxin is considered?
A2)Type B, the patient was not on a supratherapeutic cumulative dose (normal dose)
Subtype? Immune-allergic idiosyncratic toxin

Q3) What is the likely hepatotoxic pattern inflicted by the drug?
A3) Viral hepatitis

A hypercholestrolemic 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 flu; for which he was given acetaminophen for muscle aches and nasal drops for his nasal congestion.
Lab investigations shows severe elevation in ALP and no significant elevation in ALT

Q1) Which one of the following drug is the likely cause of his symptoms?
a. Nadolol b. Chlorpropamide c. Acetaminophen d. Statins
A1) B

Q2) Which type of hepatotoxin is considered?
A2) Type B, idiosyncratic hepatotoxicity

Q3) What is the hepatotoxic pattern inflicted by the drug?
A3) Inflammatory cholestasis

MCQ

1.A 17-year-old girl complained to her physician of Yellowish discoloration of skin, dark urine, rash.she was diagnosed with streptococcal pharyngitis, and treatment with erythromycin was started. her alkaline phosphatase (ALP) was markedly raised. Which of the following best explains the most likely reason for her symptoms?			
A.inflammatory Cholestasis	B. Viral hepatitis	C. inflammatory Pancreatitis	D. Cold 19
2.An 18-year-old woman presents to the Emergency Department with symptoms of nausea and vomiting. She states that she had been feeling very frustrated and upset and had taken an intentional overdose involving 50 paracetamol tablets 3 h earlier?			
A.Hepatocellular	B. Cholestatic	C. Mixed	D.Hypersensitivity or Immunologic reactions
3. Metabolic idiosyncratic hepatotoxicity is caused by?			
A.Acetaminophen	B. Amiodarone	C. Corticosteroids	D. Alcohol
4. Which of the following drugs causes cholestasis type of liver injury as a side effect?			
A. Amiodarone	B. Carbamazepine	C. Erythromycin	D. Isoniazid
5. Which of the following intrinsic hepatotoxins causes centrilobular necrosis and can be treated with N-acetylcysteine?			
A.Acetaminophen	B.Statins	C. Amiodarone	D.Phenytoin

1:A ,2:A ,3:C ,4:C ,5:A

SAQ

01

A 43-year-old woman presents to the Emergency Department after an overdose of sodium valproate, Which one of the following is the best initial treatment?

L- carnitine

02

Enumerate the lines of treatment in case of drugs hepatotoxicity

1. Immediate withdrawal of any suspected drug
2. No specific treatment
3. Specific antidotes
4. Emergency liver transplantation

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