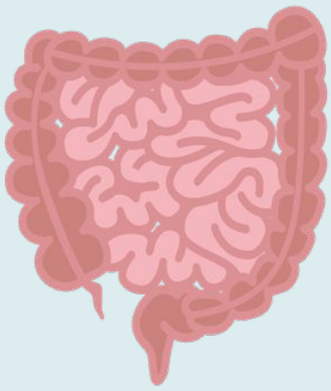
Revised & Approved

Bassam Alasmari
Rania Almutiri

Pharmacology 439

MED439



Gastrointestinal Block

Pharmacology Team 439

Helpful video

Color index:

Main Text

Important

Dr's Notes

Female Slides

Male Slides

Extra

Hepatotoxic Drugs

Objectives:

1- Define the role of liver in drug detoxification
2- Discuss the types (patterns) of hepatotoxicity
3- Classify hepatotoxins
4- Explain how a drug can inflict hepatotoxicity
5- State the pathological consequences of hepatic injury
6- Contrast the varied clinical presentation of hepatotoxicity
7- Enlist the possible treatment

Editing file | Summary

Liver Functions

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

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.

In case of the drugs:

Human body identifies almost all drugs as foreign substances i.e. XENOBIOTIC → **Has to get rid of them** → By which mechanism? **METABOLIC CLEARING HOUSE**

Drugs Metabolism

Metabolism of Drugs in the Liver:

- Liver subjects drugs to chemical transformation (metabolism) to become inactive and easily excreted.
- Since most drugs are lipophilic (can cross the lipid membrane) 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:

01 Phase 1 Reaction

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

Yields:[1]
Yields intermediates → polar, transient, usually highly reactive → far more toxic than parent substrates → may result in liver injury [Drug-Induced Liver Injury (DILI)]

02 Phase 2 Reaction

Reactions:
Conjugation with a moiety (acetate, a.a., glutathione, Glucuronic a., sulfate)

Yields:[1]
Yields products of increased solubility:
- If of high molecular weight → excreted in bile.
- If of low molecular weight → to blood→ excreted in urine.

1) What are the characteristics of this phase?

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)

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) (more toxic) in the first stage, before being conjugated for elimination (second stage)

[Drug (Pro-toxin) → Toxin→ Injury]

Example:

Paracetamol(protoxin) → CYT P450 → NAPQI (toxin) → 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**

Not all drugs can cause, hepatotoxicity so why do some drugs can cause it?

- 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 ADRs

Very important

1- Intrinsic hepatotoxin

Causes Direct hepatotoxicity.

- Inflicted by:

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

- Belong to **type A** ADRs:
  - ○ Predictable/direct
  - ○ Dose-*Dependant* hepatotoxicity

2- Idiosyncratic hepatotoxin

Causes Indirect hepatotoxicity

- Inflicted by: Normal dose.

- Belong to **type B** ADRs:
  - ○ Bizarre/Unpredictable /idiosyncratic (unusual).
  - ○ Dose-*Independent* hepatotoxicity.

Drugs that causes Intrinsic hepatotoxin (Type A)

Increased Dose	Cumulative Dose	Both
• Acetaminophen (paracetamol) • Salicylates (Aspirin) • Statins	• Amiodarone • Oral contraceptive	• Methotrexate • Alcohol

Drugs that causes 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[1] to induce a variety of immune reactions.

1) A 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

Immunologic-idiosyncratic Hepatotoxicity		Metabolic-idiosyncratic Hepatotoxicity	
Inflammatory cholestasis	**Viral hepatitis-like pattern**	**Interfere with bilirubin**	**Interfere with protein synthesis**
• Chlorpromazine[2] • Chlorpropamide[3] • 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"

2) Antipsychotic
3) Antihyperglycemic agent

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

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 Ca^{2+} homeostasis.
6- Protein synthesis inhibition.

Covalent interaction

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.

Do hepatotoxins cause liver disease in all people?

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

Environmental host Factors

- **Age**
- **Sex**
- **Disease**
- **Race**
- **Nutritional status**
- **Concomitant habits**
- **Drugs**

Host genetic makeup

- **Metabolizing enzymes**
- **Detoxifying system**
- **Drug transport**

Drug-Induced Hepatic Injury (DIHI)

AKA Drug-Induced Liver Injury (**DILI**)

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	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 Susceptibles predisposing factors	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**

1- Latency Period

Short (hrs/days)	**Direct** dose-dependent hepatotoxicity: Latency period is short as it occurs after a threshold of toxicity is reached. **E.g. acetaminophen (toxic dose)**
Intermediate (1-8ws)	**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)**
Long (1-12ms)	**indirect** metabolic idiosyncratic hepatotoxicity: latency period is usually long, unpredictable and most problematic **E.g. tetracycline, oral contraceptives**

2- Clinical pattern

The clinical presentation could be of variable intensity, ranging from asymptomatic slightly increased liver enzymes to fulminant[1] hepatic failure.

A) drugs induce symptomatic manifestations

Hepatic Injury	Hepatocellular	Cholestatic	Mixed
How They Develop *Type of enzyme increased is important *it's important to differentiate between hepatocellular & cholestatic (signs and symptoms)	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, 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
E.g. Important	- Acetaminophen - NSAIDs - Isoniazid - Amiodarone	- Chlorpropamide - Erythromycin - Rifamycin - Oral contraceptives	- Phenytoin - Carbamazepine - Sulfonamides - ACE inhibitors

[1] Sudden

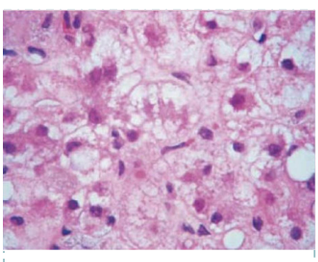
[2] Cholestasis: is defined as a decrease in bile flow due to impaired secretion by hepatocytes or to obstruction of bile flow through intra-or extrahepatic bile ducts.(team 438)

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

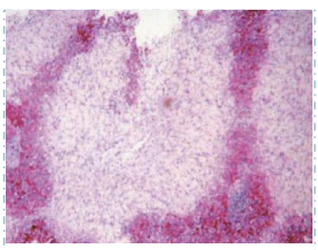
- Phenytoin
- Statins
- Sulfonamides
- Sulfonylureas

3- Histological Patterns

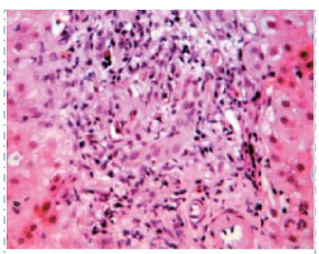
- No universal histopathological pattern of DIHI exist (nonspecific); the commonest are:
  a. Hepatocellular necrosis b. Cholestasis c. Steatosis
- More than one type of injury may occur in the same patient
- Any one agent may produce different types of injury in different patient



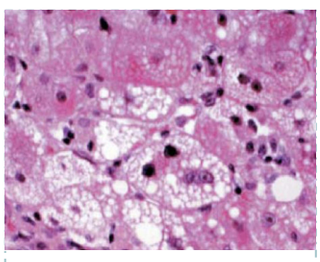
Ballooning (تضخم) & degeneration of hepatocytes



Centrilobular* & midzonal necrosis
*because CYP enzymes are concentrated here



Cholestatic injury with damaged bile duct



Fatty accumulation

Lines Of Treatment

Immediate withdrawal	Of any suspected drug (first thing to do)	
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 (NAC) for acetaminophen aka paracetamol. NAC is a precursor of glutathione, it increases the concentration of glutathione available for the conjugation of NAPQI (paracetamol toxin). - L-carnitine for valproate toxicity	
Emergency liver transplantation	For any drug induced fulminant hepatic failure	

Cases From Dr's Slides

Q1

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.

1 **What is the type of injury?**

a) Hepatocellular (hepatocytes) B) Cholestatic (biliary system)

2 **Which one of the following drugs is the likely cause of her symptoms?**

a. Cyclosporine b. Multivitamins
c. Isoniazid d. Domperidone

3 **Which type of hepatotoxin is considered?**

Type B, the patient was not on a supratherapeutic cumulative dose (normal dose)
Subtype? Immune-allergic idiosyncratic toxin

4 **What is the likely hepatotoxic pattern inflicted by the drug?**

Viral hepatitis

Q2

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

1 **Which one of the following drug is the likely cause of his symptoms?**

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

2 **Which type of hepatotoxin is considered?**

Type B idiosyncratic hepatotoxicity

3 **What is the hepatotoxic pattern inflicted by the drug?**

Inflammatory cholestasis

Summary

Dr: It's Important to know how to differentiate between type A and Type B (the drugs that induce each of them), which level of enzyme increases in which condition, the signs and symptoms, all the examples are **important**

Types of Drug-Induced Hepatotoxicity	
Type A (Direct)	**Type B (Indirect)**
- Intrinsic hepatotoxin - Supratherapeutic/cumulative dose - Predictable - Dose-dependent	- Idiosyncratic hepatotoxin - Normal dose - Unpredictable - Dose-independent

Clinical Patterns of Drugs induced hepatotoxicity			
Injury	**Hepatocellular**	**Cholestatic**	**Mixed**
How They Develop	If injury targets hepatocytes → apoptosis or necrosis → HEPATITIS develops → rapid onset of malaise, severe anorexia and jaundice + ↑ in alanine aminotransferases (ALT)	If injury targets biliary system →CHOLESTASIS develop → jaundice +\- severe pruritus predominate → ↑ in alkaline phosphatase (ALP) +\- hyperbilirubinemia	if injury targets both hepatocytes & biliary system→ MIXED TYPE.
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) are present
↑ Enzymes	ALT only	ALP only	Both ALT & ALP increase
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

Treatment	
Non-specific treatment	**Specific antidotes**
- Corticosteroids for severe allergic reactions - Cholestyramine for pruritus - Ursodeoxycholic acid (Ursodiol) for cholestatic liver injury	- N-acetylcysteine for acetaminophen toxicity - L-carnitine for valproate toxicity

Summary

Classification	Drugs
Hepatocellular pattern	1. Acetaminophen 2. NSAIDs 3. Isoniazid 4. Amiodarone
Cholestatic pattern	1. Chlorpropamide 2. Erythromycin 3. Rifamycin 4. Oral contraceptives
Mixed pattern	1. Phenytoin 2. Carbamazepine 3. Sulfonamides 4. ACE Inhibitors
Type A (Increased Dose)	1. Acetaminophen (paracetamol) 2. Salicylates (Aspirin) 3. Statins
Type A (Cumulative Dose)	1. Amiodarone 2. Oral contraceptive
Type A (increased and cumulative Dose)	1. Methotrexate 2. Alcohol
Type B Immunologic-idiosyncratic Hepatotoxicity	**Inflammatory cholestasis** 1. Chlorpromazine 2. Chlorpropamide 3. Erythromycin
	Viral hepatitis-like pattern 1. Isoniazid 2. Phenytoin 3. Methyldopa
Type B Metabolic-idiosyncratic Hepatotoxicity	**Interfere with bilirubin** 1. Erythromycin 2. Rifampicin
	Interfere with protein synthesis 1. Corticosteroid 2. Tetracycline

MCQs

Q1: A 43-year-old man has heterozygous familial hypercholesterolemia. His serum concentrations of total cholesterol and LDL are markedly elevated. After being counseled about lifestyle and dietary changes, the patient was started on atorvastatin. During his treatment with atorvastatin, it is important to routinely monitor serum concentrations of which of the following?			
A- Blood urea nitrogen	B- ALT,AST	C- Platelets	D- Uric acid
Q2: Depending on your answer in the previous question, Which type of hepatotoxin is considered?			
A- Intrinsic hepatotoxin (TypeA)	B- Idiosyncratic hepatotoxin (Type B)	C- :)	D- :)
Q3: 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- covid19
Q4: Depending on your answer in the previous question, Which one of the following is the best initial treatment?			
A- Corticosteroids	B- Cholestyramine	C- Ursodeoxycholic acid (Ursodiol)	D- Higher dose of erythromycin
Q5: 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
Q6: Depending on your answer in the previous question, Which one of the following is the best initial treatment?			
A-Propranolol	B- Adenosine	C- N-acetylcysteine	D- L-carnitine
Q6: 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?			
A- Propranolol	B- Adenosine	C- L-carnitine	D- N-acetylcysteine

1	2	3	4	5	6	7
B	A	A	C	A	C	C

SAQ

Q1) You are asked to see a 78-year-old man, a nursing-home resident who has recently moved into the care home due to progressive Alzheimer's disease. He has had several subacute confusional episodes since his arrival, for which the duty GP has been called twice in the past month, and he has been prescribed an antipsychotic (chlorpromazine) to reduce his agitation. Past history of note includes previous alcoholism and an episode of biliary colic many years ago. He reports no abdominal pain. On examination he is deeply jaundiced. On blood testing, his alkaline phosphatase (ALP) activity and bilirubin concentration are markedly raised.

a) **Which type of hepatotoxin is considered?**
b) **What is the hepatotoxic pattern inflicted by the drug?**
c) Name three other drugs that can cause the same condition?

Q2) Q3) A 78-year-old man was admitted to the hospital because of Flu-like symptoms, malaise, muscle aches weakness, loss of appetite,diarrhea, jaundice ,urine discolored The man had been receiving an antiarrhythmic drug for 2 months to treat refractory supraventricular tachycardia. On blood testing, his Alanine aminotransferase (ALT) activity was markedly raised.

a) What drug was mostly prescribed to the patient?
b) **Which type of hepatotoxin is considered?**
c) **What is the hepatotoxic pattern inflicted by the drug?**
d) Name three other drugs that can cause the same condition?

A 76-year-old woman from a nursing home presented to the emergency department with a change in her mental state over the past few hours. She had a medical history of hypertension. Her medications included captopril (ACEI), on physical examination she showed Flu-like symptoms,Yellowish discoloration of skin, pruritus,cough,diarrhea.
On blood testing, his Alanine aminotransferase (ALT) and alkaline phosphatase (ALP) activity are markedly raised.

a) **What is the hepatotoxic pattern inflicted by the drug?**
b) Name three other drugs that can cause the same condition?

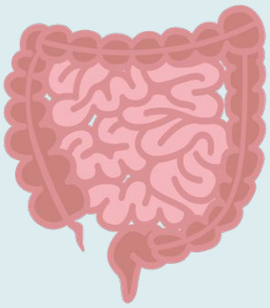
Answers

A1) a) Type B immunologic idiosyncratic hepatotoxin b) cholestatic liver injury. c) 1. Chlorpropamide 2. Erythromycin 3. Rifamycin

A2) a) Amiodarone b)Intrinsic hepatotoxin (Type A) (cumulative dose) c) Hepatocellular injury d) 1. Acetaminophen 2. NSAIDs 3. Isoniazid

A3) a) Mixed hepatocellular and cholestatic b) 1. Phenytoin 2. Carbamazepine 3. Sulfonamides

Feedback Form



Gastrointestinal Block

Pharmacology Team 439

Leaders

Banan AlQady

Ghada AlOthman

Nawaf Alshahrani

Organizers

- Ghada Aljedaie
- Hind Almotywea
- Mais Alajami
- Norah Alasheikh
- Nouf Alsubaie
- Sadem Alzayed
- Shatha Aldhohair
- Shayma Alghanoum
- Tarfa Alsharidi

Note Takers

- Duaa Alhumoudi
- Homoud Algadheb
- Mishal Althunayan
- Omar Alhalabi
- Yasmine Alqarni

Revisers

- Dana Naibulharam
- Mishal Althunayan
- Omar Alhalabi

Members

- Abdulaziz Alderaywsh
- Abdulaziz Alghuligah
- Abdulrahman Almebki
- Abdulrhman Alsuhaibany
- Aljoharah Albnyan
- Aljoud Algazlan
- Arwa alqahtani
- Feras Alqaidi
- Lama Alahmadi
- Maha Alanazi
- Manal Altwaim
- Mona Alomiriny
- Norah Almasaad
- Noura Bamarei
- Rand AlRefaei
- Rawan Bakader
- Salem Alshihri
- Shahd Almezel