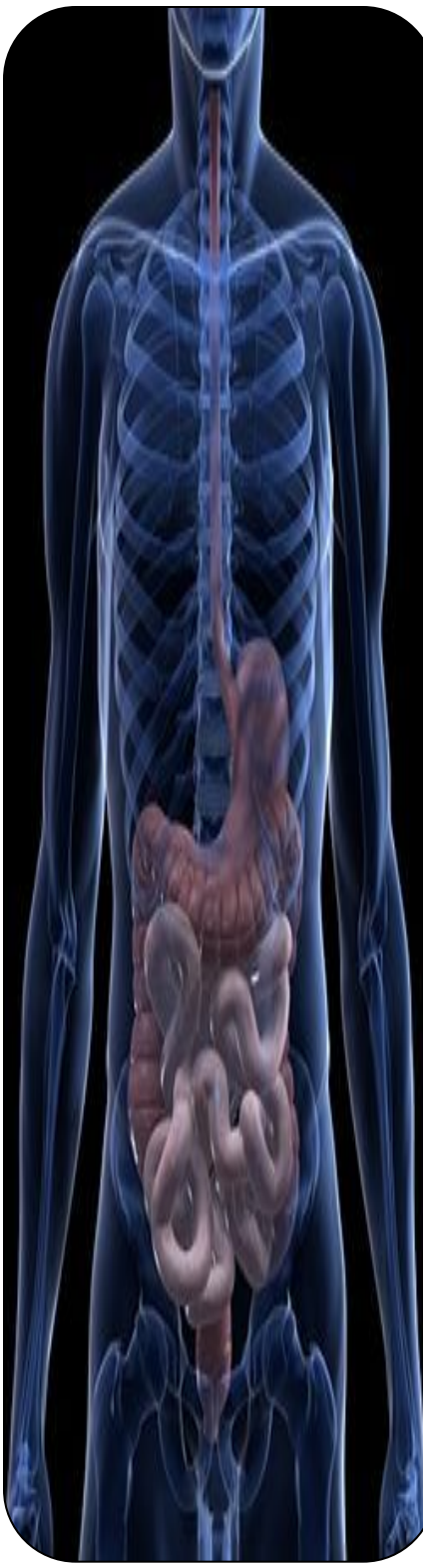

Pharmacology Team

Hepatotoxic drugs

Done by:

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- **BLUE: team notes**
- **RED: very important**
- **GREY: not important "they will not ask about it in the exam"**

Other than that is just a format

The Liver Subjects drugs to chemical transformation (METABOLISM) → to become inactive & easily excreted. Since most drugs are lipophilic → they are changed into hydrophilic water soluble products →suitable for elimination through the bile or urine through kidneys.

Such metabolic transformation usually occurs in 2 PHASES:

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

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** 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 "eg: panadol"	$\xrightarrow{CYT\ P450}$	NABQI (more toxic than the pro drug "paracetamol")	→	centrilobular 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 …etc

Type of hepatotoxins and the hepatotoxicity inflicted:

Type of hepatotoxicity inflected	The drug(hepatotoxin) type	The hypotoxicity type	The type of ADRS
1-Supertherapeutic dose **2-Cummulative dose**	**Intrinsic hepatotoxin** (the drug is converted into its toxic form in the body)	**Direct hepatotoxicity**	**Type A** ADRs/predictable/ direct
Normal dose	**Idiosyncrtic hepatotoxin**	**Indirect hepatotoxicity**	**Type B** ADRs / bizarre / unpredictable/idiosyncratic

1- Direct hepatotoxicity caused by intrinsic hepatotoxin:

***Type A:** Dose-dependent hepatotoxicity

Direct dose dependent hepatotoxicity	Acetaminophen Statins	Increased Dose
Direct cumulative hepatotoxicity	Amiodarone Oral contraceptives	Cumulative Dose

2-Indirect hepatotoxicity caused by idiosyncratic hepatotoxin:

TYPE B: Dose-independent hepatotoxicity, divided into:

a) Hypersensitivity (immunoallergic reactions)

b) Metabolic-idiosyncratic reactions

2.a) Immunoallergic Idiosyncratic Hepatotoxicity:

Drug or its metabolite binds to hepatic membranes or proteins → act as hapten to induce a variety of immune reactions:

Inflammatory cholestasis	Viral hepatitis-like pattern
Chlorpromazine. Chlorpropamide. Erythromycin.	Isoniazid. Phenytoin. Methyldopa.

* cholestasis is a condition where bile cannot flow from the liver to the duodenum.

2.b) Metabolic Idiosyncratic Hepatotoxicity :

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

Interfere with bilirubin metabolism	Interfere with protein synthesis
It causes cholestasis like symptoms (Damaging the biliary system)	It causes hepatocellular damage – viral hepatitis like symptoms
Erythromycin Rifampicin	Corticosteroids Tetracycline

N.B. Not all drugs fall neatly into one of these categories, and overlapping mechanisms may occur with some drugs.

eg: it erythromycin could be classified as metabolic causes or immunological causes

How can a drug induce hepatotoxicity?

Prof.Omnia said: this is pure biochemistry so, read it for your knowledge "they will not ask about it".

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:**
  - It is adduct formation between the metabolite of the drug & cellular macromolecules
  - If covalent binding to **protein** è immunogenic reaction
  - If binding to **DNA** è carcinogenesis
- **Non-covalent interactions:**
  - **Lipid peroxidation** è generation of cytotoxic **oxygen radicals**
  - Impairment of mitochondrial respiration
  - Depletion of **GSH(glutathione)** reactions è 'oxidative stress'
  - Modification of sulfhydryl groups è impair Ca2+homostasis
  - **Protein synthesis** inhibition

What are the presenting manifestations?

Individual drugs tend to have Characteristic signature, composed of:

- A particular latency period
- A clinical pattern
- A particular pathological finding

LATENCY PERIOD:

short (hours/days), intermediate (1-8weeks), long (1-12monthes)

- **Direct dose-dependent Hepatotoxicity:**
  Latency period is **SHORT** as it occurs after a threshold of toxicity is reached e.,g : **acetaminophen (Paracetamol)** (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 , most problematic (it takes months to years and may cause carcinogenesis) e.g : tetracyclines, oral contraceptives

CLINICAL PATTERNS:

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

* **Some drugs just induce: Asymptomatic** ↑ In Aminotransferases

- Phenytoin
- Statins
- Sulfonamides
- Sulfonylureas

*** Other drugs induce Symptomatic manifestations**

- **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 **pruritis "itching"** predominate +↑ **in alkaline phosphatase (ALP) + hyperbilirubinaemia**
- **If injury targets both hepatocytes & biliary system: Mixed type**
- **Pruritus is the primary symptom of cholestasis and is thought to be due to interactions of serum bile acids with the skin (bile is irritant to the skin in high concentrations).**

Some patterns of symptomatic drug-induced liver disease:

Hepatic injury	Hepatocellular	Cholestatic	Mixed
	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**	
ALT	**≥ 3 fold rise**	**Normal or slight**	**≥ 3 fold rise**
ALP	**Normal**	**≥ 2 fold rise**	**≥ 2 fold rise**
Examples	**Acetaminophen NSAIDs Isoniazid Amiodarone**	**Chlorpropamide Erythromycin Rifamycin Oral contraceptives**	**Phenytoin Carbamazepine Sulfonamides ACE Inhibitors**

Case 1 :

A long standing rheumatoid arthritis patient developed tuberculosis 2 month ago. Today she was received in E.R complaining of **yellowish discoloration of skin, severe anorexia, vomiting and flue 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 arthiritic exacerbations. **A month ago (latency period),** 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.

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

  a. Cyclosporine b. Multivitamines
  c. Isoniazid √ d. Domperidone

- **Which type of hepatotoxin is it considered?**

  Indirect Immunoallergic Idiosyncratic Hepatotoxin

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

  Viral hepatitis-like pattern
- **Treatment. "will be mentioned later"**

Case 2 :

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 **for long** receiving **statins** for the hypercholestrolemia. **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 **acetominophen** for muscle aches and **nasal drops** for his nasal stuffiness.
Lab investigations shows severe **elevation in ALP** and no significant elevation in ALT.

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

a. Nadolol **b.Chlorpropamide √**
c. Acetominophen d. Statins

Note: Statins , Acetominophen , and Chlorpropamide all are **heptatotoxins** BUT, **Statins** causeS an **asymptomatic increase in liver enzymes**, the **Acetaminophen** causeS **hepatitis like symptoms**, and **Chlorpropamide** cause **cholestatic injury** .

- **Which type of hepatotoxin it is considered?**
  Indirect Immunoallergic Idiosyncratic Hepatotoxin.

- **What is the hepatotoxic pattern inflicted by the drug?**
  Inflammatory cholestasis pattern.
- **Treatment. "will be mentioned later"**

What are the lines of treatment?

- **Immediate withdrawal of any suspected drug**
- **No specific treatment:**
  - **Symptomatic;**
    - If a **severe allergic reaction** (not pruritus) is observed : **Corticosteroids**
    - If **pruritus** : **Cholestyramine** which **enhance bile acid excretion**
    - **If cholestatic liver injury : Ursodeoxycholic acid (Ursodiol)**
    - If coagulopathy or encephalopathy develop : treat accordingly
  - **Supportive; (not imp)**
    High carbohydrate, moderate protein diet adequate in calories
- **Specific antidotes :**
  - **N-acetylcysteine to treat acetaminophen (paracetamol) toxicity.**
  - NAPQI (the metabolite of paracetamol) normally is conjugated by glutathione, when taken in excess, the body's glutathione reserves are not sufficient to inactivate the toxic NAPQI. So how to treat?
    By N-acetylcysteine which is derivative of the antioxidant amino-acid cysteine (cysteine is the precursor of the antioxidant glutathione).
  - **L-carnitine: valproate toxicity**
- **Emergency liver transplantation:**
  for drug induced fulminant hepatic failure

Summary

- Paracetamol (acetaminophen) is pro-toxin that may convert by CYP450 to NABQI (TOXIC) which causes centrilobular injury when excess
- Supertherapeutic or cummulative dose of the drug > INTRINSIC HEPATOTOXIN > DIRECT HEPATOTOXICITY > belong to TYPE A ADRs: PREDICTABLE / DIRECT e.g. : Acetaminophen , Statins
- If the toxicity is inflicted by normal dose of the drug > IDIOSYNCRTIC HEPATOTOXIN > INDIRECT HEPATOTOXICITY > belong to TYPE B ADRs: UNPREDICTABLE / BIZZAR / IDIOSYNCRATIC e.g. : Chlorpropamide ,Isoniazid
- If heptotoxin drug form covalent binding with protein that will change the structure of protein resulting in immunogenic reaction
- The hepatotoxin drugs have different latency period before the symptoms appear the hepatotoxin that cause (Direct dose-dependent Hepatotoxicity) have short latency period however the hepatotoxin drugs which cause Direct cumulative or In Indirect Immunoallergic Idiosyncratic Hepatotoxicity have intermediate latency period , while the hepatotoxin drug that cause Indirect Metabolic Idiosyncratic Hepatotoxicity e.g. : tetracycline and oral contraceptive have longer latency period
- Phenytoin , Statins , Sulfonamides and Sulfonylureas are hepatoxin drugs that can rise liver enzyme without clear symptoms on the patient (asymptomatic = Silenyt)
- If injury targets hepatocytes rapid onset of malaise, severe anorexia and jaundice + increase in alanine aminotransferases (ALT) can be caused by Acetaminophen ,NSAIDs ,Isoniazid and Amiodarone
- If injury targets biliary system (canalicular or ductal) : jaundice + severe pruritis predominate + increase in alkaline phosphatase (ALP) + hyperbilirubinaemia it can be caused by Chlorpropamide ,Erythromycin , Rifamycin and Oral contraceptives
- Phenytoin , Carbamazepine , Sulfonamides and ACE Inhibitors cause mixed injury (hepatitis and cholestasis)
- No specific treatment for hepatotoxicity but there is specific antidotes e.g. : N-acetylcysteine to treat acetaminophen toxicity and L-carnitine for valproate toxicity

Questions :

1- baby with flu like symptoms (malaise , weakness , muscle ache . etc) , loss of appetite , diarrhea , dark urine and jaundice . History reveals that he has ingested lots of panadol tablets. Which of the following is the mechanism of the drug causing these symptoms ?

a) Direct cumulative hepatotoxicity
b) Direct dose dependent hepatotoxicity
c) Immunoallergic idiosyncratic hepatotoxicity
d) Metabolic idiosyncratic hepatotoxicity

2- what should be the treatment (antidote) of the previous baby situation ?

a) Acetyl-salicylate
b) N-acetylcystiene
c) L-carnitine
d) Cholestyramine

3- which of the following drugs can cause mixed hepatic and biliary damage?

a) phenytoin
b) isoniazid
c) sulfonylurea
d) A and C

4- patient comes to you with severe pruritus , he told you that has just started taking erythromycin before he comes. you expect the LFTs to be :

a) elevated ALP and normal ALT
b) elevated ALP and reduced AST
c) elevated ALT and normal ALT
d) elevated both ALT and ALP

Answers : b,b,a,a

GOOD LUCK