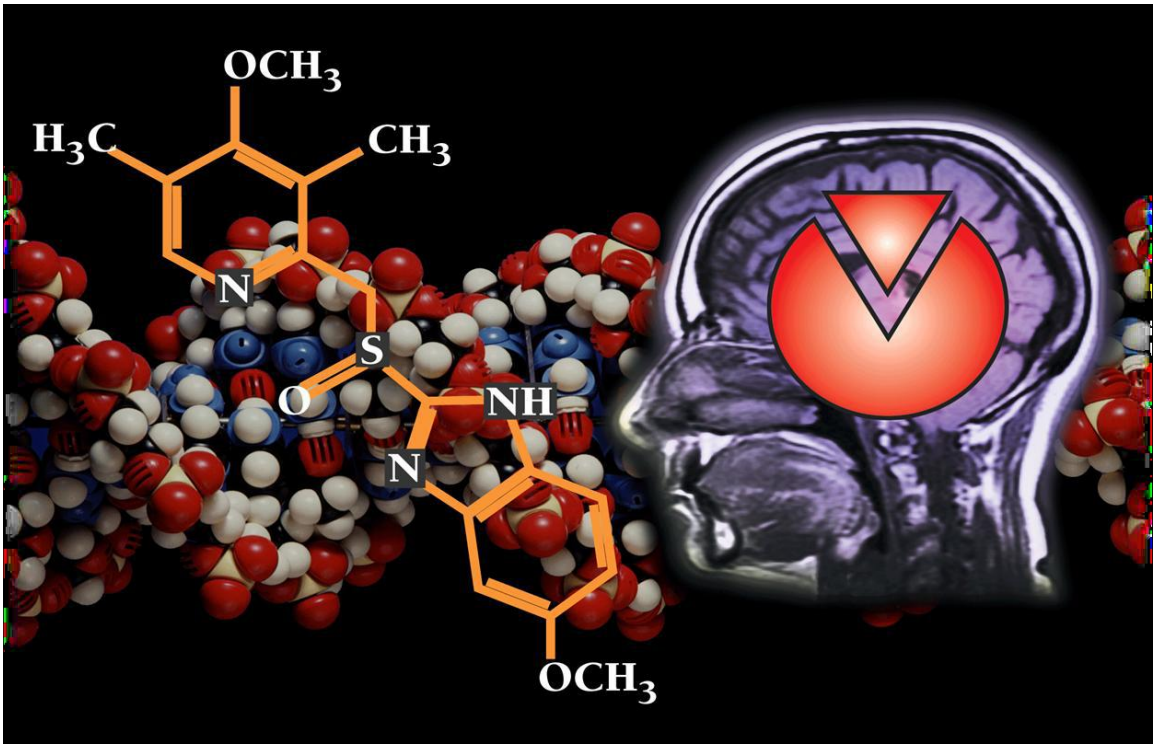
King Saud University
College Of Medicine
Pharmacology Team 430
GIT Block

Hepatotoxic Drugs



Notes in **maroon margins are additional info**

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Hepatotoxic drugs

- **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

Note: Phase II reactions are synthetic reactions that involve **addition (conjugation)** of subgroups to –OH, $–NH_2$, and –SH functions on the drug molecule. The subgroups that are **added** include **glucuronate**, acetate, glutathione, glycine, sulfate, and methyl groups. **Glucuronidation** is the most common and the most important conjugation reaction.

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 centrilobular

NAPBQI): N-acetyl-p-benzoquinone imine

Type of hepatotoxins and the hepatotoxicity inflicted

Dose	The drug(hepatotoxin) type	The hypotoxicity type	The type of ADRS
1-Supertherapeutic 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	**Increased Dose**
Salicylates	**Increased Dose**
Statins	**Increased Dose**

INTIRINSIC HEPATOTOXINS is predictable ADRS because the toxicity depends on the amount of the dosage (so we can predict the occurrence of toxicity)

Direct cumulative hepatotoxicity

Amiodarone	**Cumulative Dose**
Oral contraceptives	**Cumulative Dose**
Methotrexate	**Increased & Cumulative dose**

Some time not all the amount of the drug will be execrated so it accumulates in the body ➔**toxicity occur** within the long usage**.**

Direct cumulative + Direct dose dependent hepatotoxicity

Alcohol	**Increased & Cumulative dose**

2-.Indirect hepatotoxicity caused by idiosyncratic hepatotoxin

TYPE B: Dose-independent hepatotoxicity ➔ divided into:

- **Hypersensitivity (immunoallergic reactions)**
- **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.	**Isoniazid.**
Chlorpropamide.	**Phenytoin.**
Erythromycin.	**Methyldopa.**

❖ 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 (it causes cholestasis like symptoms) (Damaging the **biliary** system)	Interfere with protein synthesis (it causes **hepatocellular damage** – viral hepatitis like symptoms)
Erythromycin	**Corticosteroids**
Rifampicin	**Tetracycline**

N.B. Not all drugs fall neatly into one of these categories, and overlapping mechanisms may occur with some drugs eg: **erythromycin i**t could be classified as metabolic causes or immunological causes

How can a drug induce hepatotoxicity?

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** ➔ immunogenic reaction
- If binding to **DNA** ➔ carcinogenesis

Strong binding of the drug with protein→change the structure and the shape of protein →body will attack the self protein as a foreign substance (immunological reaction)

Non-covalent interactions:

- **Lipid peroxidation** ➔ generation of cytotoxic **oxygen radicals**
- Impairment of mitochondrial respiration
- Depletion of **GSH(glutathione)** reactions ➔ 'oxidative stress'
- Modification of sulfhydryl groups ➔ impair Ca^{2+}homostasis
- **Protein synthesis** inhibition

Glutathione (**GSH**) is a tripeptide that function as an antioxidant, preventing damage to important cellular components caused by reactive oxygen species such as free radicals and peroxides.

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: The period of time that must elapse between the time at which a dose of drug is **applied** to a biologic system and the time at which a specified **pharmacologic effect** is produced.(The side effect appears)

LATENCY PERIOD ➔ short (hrs/dys), intermediate (1-8ws), long (1-12ms)

★ **In Direct dose-dependent Hepatotoxicity** ➔Latency period is **SHORT** as it occurs after a threshold of toxicity is reached e.,g : **acetaminophen (Paracetamol)** (toxic dose)

★ **In 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** predominate → ↑ **in alkaline phosphatase (ALP) ± hyperbilirubinaemia**

* **If injury targets both hepatocytes & biliary system** : **Mixed type**

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

Note: In the cases there are either new symptoms or no improvement. The first means that there is drug toxicity due to inhibition of metabolism of the drug by another drug (inhibitor). While the second means metabolism of drug is induced by an inducer drug. However, if the patient comes with hepatitis or cholestatic like symptoms it is probably by a hepatotoxic drug.

Case 1 :

A long standing rheumatoid arthritis patient developed tuberculosis 2 month ago. Today she was received in E.R complaining of **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?**

Hepatocellular

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

Hepatitis

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**. **Statins** cause an **asymptomatic increase in liver enzymes**, the **Acetaminophen** cause **hepatitis like symptoms**, and **Chlorpropamide** cause **cholestatic injury** .

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

Injury of the biliary system

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

Cholestatic

What are the lines of treatment?

* **Immediate withdrawal** of any suspected drug

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

* 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 toxicity.**
  - **L-carnitine ➔valproate toxicity**

* **Emergency liver transplantation :** for drug induced fulminant hepatic failure

Note: acetylcysteine is indicated for the treatment of paracetamol (acetaminophen) overdose. When paracetamol is taken in large quantities, a minor metabolite called *N*-acetyl-*p*-benzoquinone imine (NAPQI) accumulates within the body. It is normally conjugated by glutathione, but when taken in excess, the body's glutathione reserves are not sufficient to inactivate the toxic NAPQI. This metabolite is then free to react with key hepatic enzymes, therefore damaging hepatocytes. This may lead to severe liver damage and even death by fulminant liver failure.

For this indication, acetylcysteine acts to augment the glutathione reserves in the body and, together with glutathione, directly bind to toxic metabolites. These actions serve to protect hepatocytes in the liver from NAPQI toxicity.

Summary

- Sometime the pro toxin drug when undergoes phase 1 become more toxic and cause liver injury eg: **Paracetamol** is pro toxin that may convert by CYP450 to **NABQI (TOXIN)** which cause centrilobular injury
- **Supertherapeutic or cummulative dose** of the drug ➔INTRINSIC HEPATOTOXIN ➔The hepatotoxicity it inflicts is ➔ DIRECT HEPATOTOXICITY ➔ belong to TYPE A ADRs: PREDICTABLE / DIRECT eg: **Acetaminophen , Statins**
- If the toxicity is inflicted by **normal dose** of the drug ➔ **IDIOSYNCRTIC HEPATOTOXIN** ➔The hepatotoxicity it inflicts is ➔ **INDIRECT HEPATOTOXICITY** ➔belong to **TYPE B ADRs**: UNPREDICTABLE / BIZZAR / IDIOSYNCRATIC eg: 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** eg: **tetracycline and oreal contraceptive** have longer latency period
- **Phenytoin , Statins , Sulfonamides and Sulfonylureas** are hepatoxin drugs that can rise liver enzyme without clear symptoms on the ptient (asymptomatic)
- If injury targets hepatocytes rapid onset of malaise, severe **anorexia** and jaundice + ↑ **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 ➔ ↑ 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 eg: N-acetylcysteine to treat acetaminophen toxicity and L-carnitine ➔for valproate toxicity