بسم الله الرحمن الرحيم

Drugs and the liver

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Effects of liver disease on Pharmacokinetic of drugs

1- Absorption and bioavailability

- Oral drugs may undergo 'first pass metabolism' by the liver before reaching the systemic circulation.
- In liver failure the degree of first pass metabolism will be **reduced**, therefore more drug will reach the systemic circulation, **thus increasing bioavailability.**
- This effect is particularly important for drugs with extensive first-pass metabolism (Drugs with high hepatic extraction ratio).

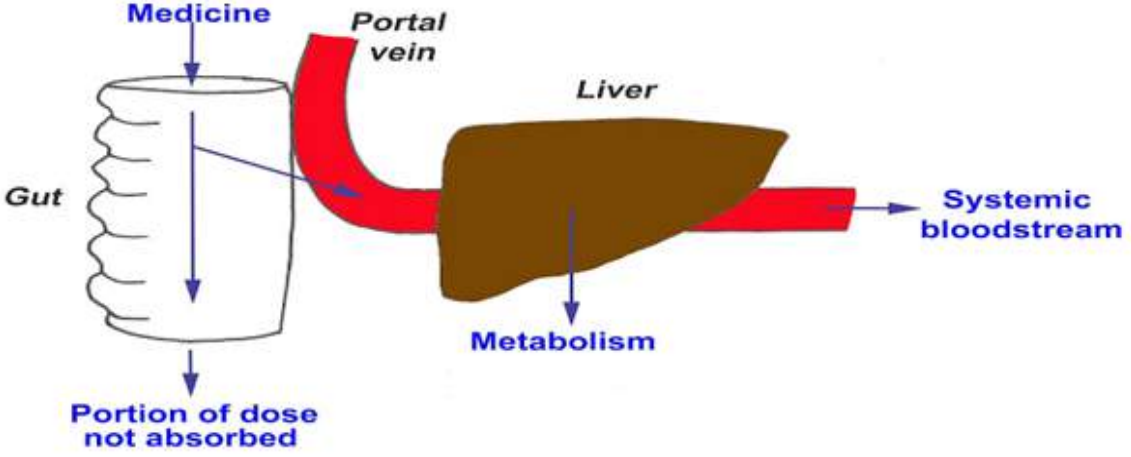
- In end-stage liver disease, a great part of blood in portal vein escapes from liver and flows straight into systemic circulation (by means of **porto-systemic shunts**).
- These shunts can affect first-pass metabolism by diminishing liver perfusion. In these cases, less drug passes through the liver before systemic distribution consequently, there is an elevation in drug concentrations in the blood (increased bioavailability).

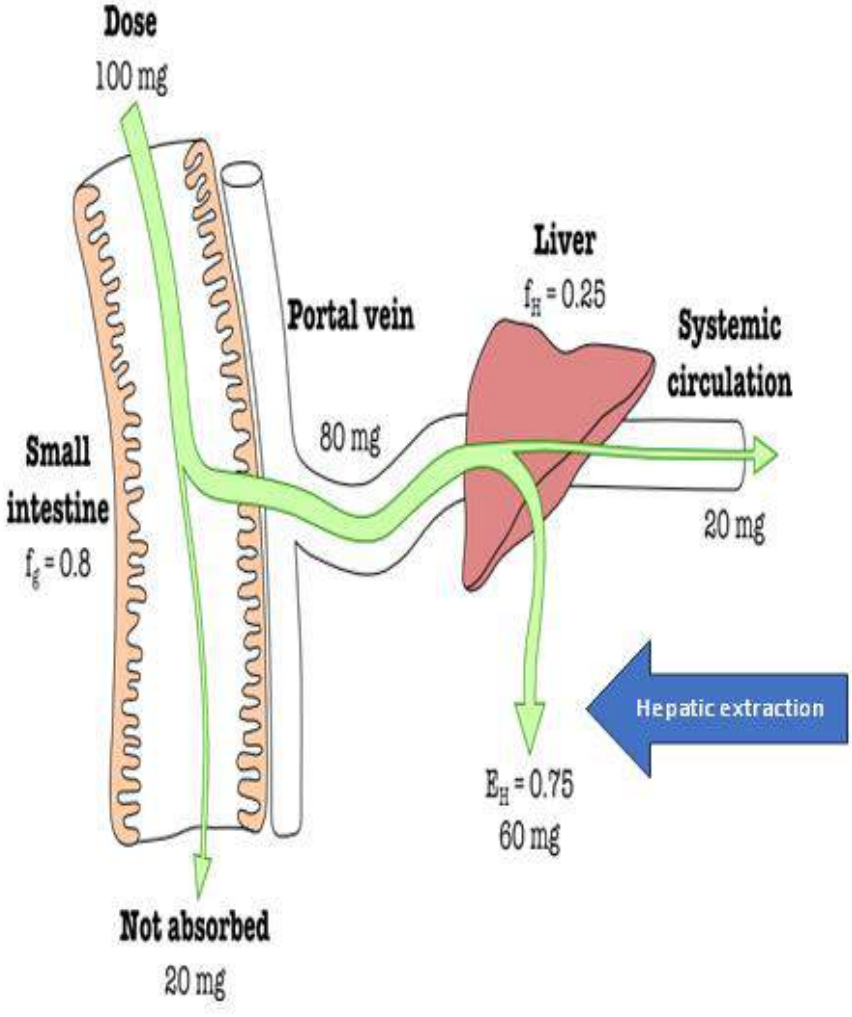
- Hepatic extraction ratio is the fraction of the drug entering the liver which is irreversibly removed (extracted) during one pass of the blood through the liver.

- **Drugs can be divided into:**

1- Drugs with **high** hepatic extraction ratios >0.7, for example propranolol, lignocaine opiates (like **fentanyl**, and **morphine**).

2- Drugs with **low** hepatic extraction ratios <0.3 such as lorazepam, diazepam and **methadone**.




Dose
100 mg
Liver
f_H = 0.25
Portal vein
Systemic circulation
80 mg
Small intestine
f_g = 0.8
20 mg
Hepatic extraction
E_H = 0.75
60 mg
Not absorbed
20 mg

2- Distribution

- In liver disease, protein synthesis may be reduced.
- In case of Cirrhosis, hypo-albuminemia occurs resulting in low albumin levels (to which most drugs bind in the plasma), thiswill cause an increased concentration of free active drug in the blood (more severe adverse effects could occur).
- Therefore, highly protein-bound drugs, such as benzodiazepines, (particularly diazepam, which is more than **99% protein** bound) may produce significant adverse effects in hepatic patients.

3- Metabolism

- Several drugs are metabolized by the liver (phase 1 and 2 reactions).
- Liver diseases can **reduce the activity of CYP450 isozymes.**

- **In phase 1**, cytochrome P-450 enzymes, are responsible for the hydrolysis, oxidation, or reduction of the drug molecule.
- For most drugs, these reactions decrease the pharmacological activity of the drug. However, drugs are sometimes metabolized into active metabolites, which is the case with some benzodiazepines, tricyclic antidepressants and antipsychotic.

- **Phase 2** (conjugation) is less affected in liver disease.
- conjugation with glucuronic acid is normally preserved in liver disease.
  - Therefore, it might be beneficial to select a drug that only requires glucuronidation, and does not require a phase 1 reaction (e.g., Olanzapine, oxazepam, and lorazepam)

- Drug metabolism by the liver may also be reduced using vasopressors on intensive care which reduce liver blood flow due to vasoconstriction.

4- Biliary excretion

In liver disease, the following may occur in relation to impairment of normal biliary secretion:

1-Drugs and metabolites which rely on biliary excretion will be retained and not efficiently excreted (toxicity could occur). These drugs may require dose adjustment.

2-Drugs with enterohepatic recirculation may have decreased half lives due to failure of recirculation.

3-High bilirubin levels may result in the displacement of drugs from albumin as it competes for binding sites.

4-Decreased secretion of bile may result in malabsorption of fat-soluble vitamins and drugs.

- Drugs with a molecular weight of **> 300 g/mol** and with both polar and lipophilic groups are more likely to be excreted in bile and subject to enterohepatic recycling.

Examples

1-Digoxin.

2- Warfarin.

3- Antibiotics (ceftriaxone, Cefoperazone, macrolides rifampicin, and others)

4-Mycophenolate mofetil.

5-Spironolactone

6-Steroid hormones (e.g., estrogen),

7-Opioids

8- NSAIDs (e.g., **diclofenac** & **indomethacin**),

9- The anticancer doxorubicin

Dose adjustment in hepatic diseases

- Unfortunately, there is no simple endogenous marker to predict hepatic function with respect to the elimination capacity of specific drugs.
- Therefore, clinicians use liver function tests, international normalized ratio (INR), serum albumin and scores such as the Child Pugh score.
- Dose adjustment is difficult and could be **not accurate** (unlike in renal impairment).

Drugs that have the following properties are less likely to need a dosage adjustment in patient with hepatic impairment.

1- The drug is metabolized in the liver to a small extent (<20%)

2- The therapeutic range of the drug is wide.

2-The drug is gaseous or volatile.

3-The drug and its active metabolites are primarily eliminated via the lungs.

For each drug , the physician needs to assess the degree of hepatic impairment and consider the known pharmacokinetics and pharmacodynamics of the drug

Anti-inflammatory drugs and the liver

- NSAIDs are contraindicated for systemic use in most liver disease patients, because:

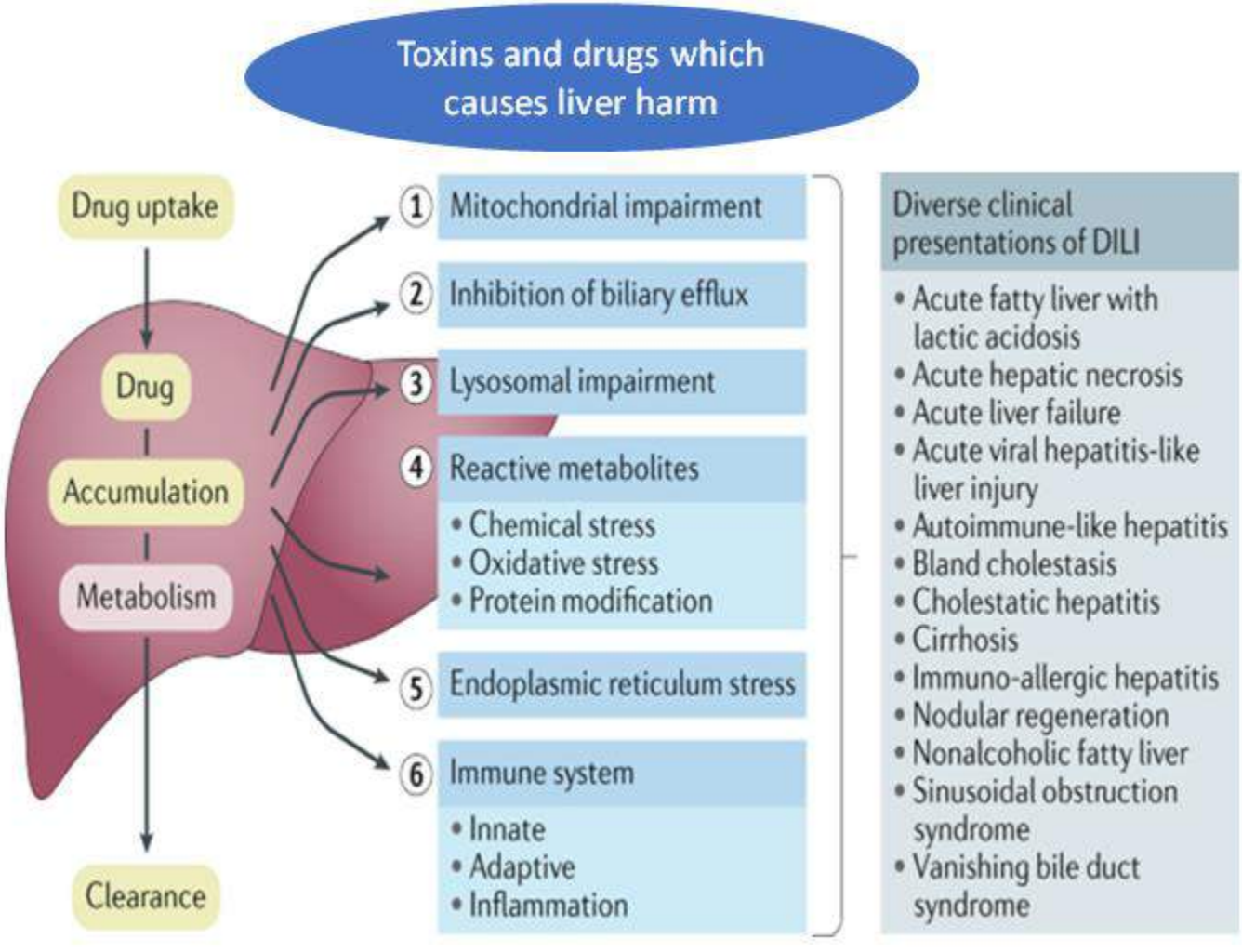
1- Most NSAIDs are **hepatotoxic**

2- **Increased adverse effects** of NSAIDs due to increased bioavailability

3- NSAIDs precipitates **gastrointestinal bleeding** in hepatic patients

4-NSAIDs precipitates **renal failure** in hepatic patients.

- Corticosteroids:
- low dose dexamethasone is probably safe in patients with chronic stable liver disease.
  - However, use of methylprednisolone in high doses may reactivate HBV and increase the risk of spontaneous bacterial peritonitis in severe cases.


Toxins and drugs which causes liver harm
Drug uptake
Drug
Accumulation
Metabolism
Clearance
1 Mitochondrial impairment
2 Inhibition of biliary efflux
3 Lysosomal impairment
4 Reactive metabolites
• Chemical stress
• Oxidative stress
• Protein modification
5 Endoplasmic reticulum stress
6 Immune system
• Innate
• Adaptive
• Inflammation
Diverse clinical presentations of DILI
• Acute fatty liver with lactic acidosis
• Acute hepatic necrosis
• Acute liver failure
• Acute viral hepatitis-like liver injury
• Autoimmune-like hepatitis
• Bland cholestasis
• Cholestatic hepatitis
• Cirrhosis
• Immuno-allergic hepatitis
• Nodular regeneration
• Nonalcoholic fatty liver
• Sinusoidal obstruction syndrome
• Vanishing bile duct syndrome

1- Fatty Liver

liver is the site of synthesis, storage, and release of lipids. **Carbon tetrachloride**, **tetracycline** and chronic **ethanol** can block the secretion of triglycerides, causing fatty liver.

2-Necrosis and Apoptosis (Liver Cell Death)

One possible cause of hepatic necrosis is *lipid peroxidation*

Carbon tetrachloride, *chloroform* , *bromobenzene* , and other *halogenated hydrocarbons* are metabolized by cytochrome P450 to form free radicals, that can bind to and damage macromolecules (Unsaturated fatty acids in hepatic cell membranes).

Troglitazone may trigger apoptosis in hepatocytes.

Paracetamol (acetaminophen) induced liver injury

Acetaminophen is metabolized to N–acetyl p-benzoquinoneimine (NAPQI).

This toxic metabolite is capable of binding to and damaging cellular macromolecules (if not conjugated with SH group of glutathione).

In the case of acetaminophen overdose (>5-6 gm/day in adults) and a glutathione depletion (in liver cirrhosis); the reactive toxic metabolite production may lead to significant necrosis and **hepatotoxicity**.

N-acetylcysteine (NAC) which contain SH groups to react with the toxic metabolite (NAPQI) is used for treating paracetamol induced liver toxicity.

3- Cholestasis and gall stones

Examples: steroids (including contraceptives), phenothiazines, and tricyclic antidepressants.

It is characterized by jaundice (yellowish discoloration of the eyes and skin) resulting from increased bilirubin levels in blood.

Clofibrate has been shown to increase the risk for gallstone formation.

4- Cirrhosis

Chronic exposure to hepatotoxic agents (e.g. Ethanol) will damage the hepatocytes & increase the activity of fibroblasts resulting in cirrhosis and fibrosis.

5- Acute Hepatitis

Exposure to the anesthetic *halothane* can cause a condition resembling viral hepatitis.

Valproic acid can cause fulminant hepatitis in children.

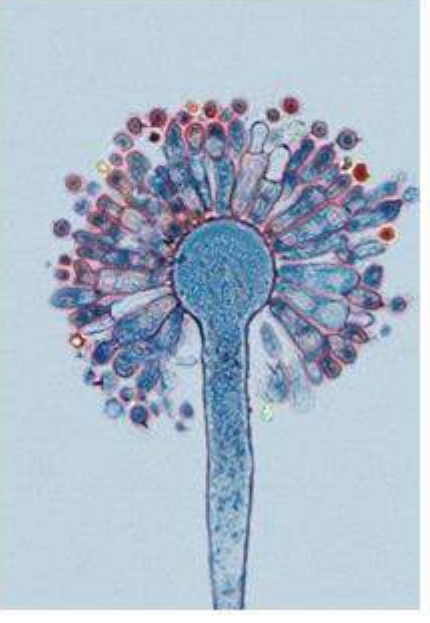
6- Carcinogenesis

Many hepatotoxicants, including carbon tetrachloride & chloroform, are hepatic carcinogens for laboratory animals.

Aflatoxins are potential hepatic carcinogens.

- ❑ These toxins are produced by a fungus that grows on grain and other foods.

- ❑ **Aflatoxin B1**, for example, is metabolized by cytochrome P450 to a reactive epoxide, which then can bind to DNA.



- ➢ A well-known human hepatic carcinogen is probably *vinyl chloride*, which causes a rare type of liver cancer known as *angiosarcoma*.

LiverTox

It is a free database that provides up-to-date, accurate, & easily accessed information on the hepatotoxic drugs