MEDICINE
KING SAUD UNIVERSITY

436 team
pharmacology

Hepatotoxic Drugs

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 various clinical presentation of hepatotoxicity
- Enlist the possible treatment

Color index

- extra information and further explanation
- important
- doctors notes
- Drugs names
- Mnemonics

Kindly check the editing file before studying this document

Introduction

physiological

- Has multiple functions (>5000)

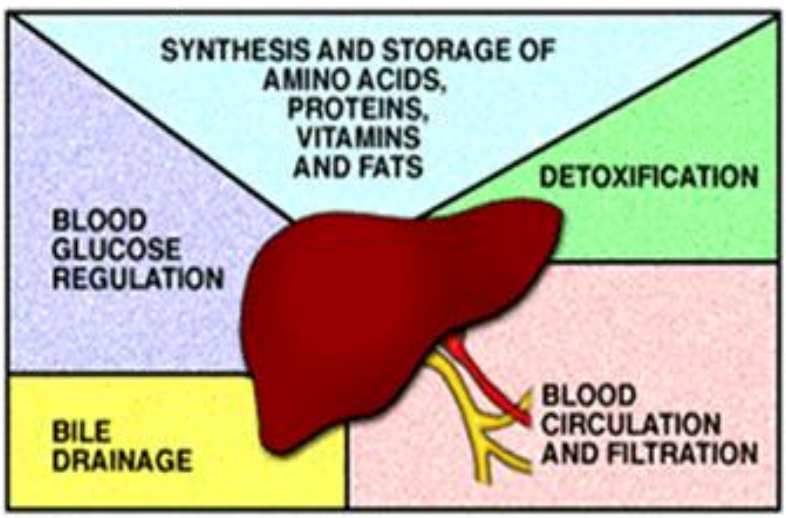
Can be categorized into:

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.

Pharmacological

drugs → Human body identifies almost all drugs as foreign substances i.e. XENOBIOTIC → Has to get rid of them

→ "METABOLIC CLEARING HOUSE"



LIVER FUNCTIONS

Introduction

- Liver subjects drugs to chemical transformation (metabolism) to become inactive and easily excreted **" convert drugs from lipophilic → Hydrophilic to excrete in urine"**
- Since most drugs are lipophilic they're changed into hydrophilic water soluble products for elimination through the bile or urine.

Such metabolic transformation usually occur 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.

Hepatotoxicity

Hepatotoxic drugs

- Hepatotoxic drugs are the leading cause of ADRs.

Hepatotoxic drugs → **drug induced liver injury** (Inflammation →Apoptosis→ Necrosis).

↓

Injury / damage of the liver is 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 ?

- 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 lead to centrilobular liver 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 (Long-acting drugs).

Hepatotoxicity

If the toxicity of HEPATOTOXIN is inflected by:

Supertheraputic / Cumulative dose of the drug
↓
INTRINSIC Hepatotoxin
- **Type** of the hepatotoxicity inflected:

↓
DIRECT hepatotoxicity
- Belong to **type A** (dose dependent) ADRs

↓
Predictable/ Direct

e.g. when we give oral anti-coagulant we predict that bleeding could be one of ADRs

Normal dose of the drug
↓
Idiosyncratic Hepatotoxin
- **Type** of the hepatotoxicity inflected:

↓ Due to hypersensitivity
INDIRECT hepatotoxicity
- Belong to **type B** (dose independent) ADRs

↓
Unpredictable/Bizzar/Idiosyncratic

e.g. when we give antibiotic and the pt. has sudden reaction to it → not predicted

Drugs that cause these types of hepatotoxicity

DIRECT increased dose dependent Hepatotoxicity	**Acetaminophen**	Increased dose
	Salicylates	
	Statins	
DIRECT cumulative Hepatotoxicity	**Amiodarone** (أمي داريه(Ami-o-darone) إني قاعد أجمع(cumulative) فلوس لبعدين)	Cumulative Hepatotoxicity
	Oral Contraceptives	
Methotrexate، Alcohol (Metho=mix)		BOTH

Type B dose dependent is divided into:

Immunoallergic idiosyncratic hepatotoxicity	Metabolic idiosyncratic hepatoxicity
A drug or its metabolite binds to **hepatic membranes or proteins** → act as hapten to induce a variety of immune reactions.	The metabolite of the offending drug interferes with hepatic metabolism as that of bilirubin or protein synthesis…etc

Drugs causing Inflammatory cholestasis:
- Chlorpromazine (Chole = Chlo)
- Chlorpropamide
- Erythromycin (كل الارث لنا = Chol eryth)

Drugs that interfere with bilirubin metabolism:
- Erythromycin (الارث كان بليون = eryth, bili=billion)
- Rifampicin (Rafeef(=rifa) is beautiful(=bili=Bella) girl. Bella in Latin and Italy mean beautiful)

Drugs causing viral Hepatitis-like pattern:
- Isoniazid anti TB (آذوا نياز وهبة = Iso-niazid & Hepa)
- Phenytoin anti epeliptic (هية فين توني شفتها!)
- methyldopa (مثل الدوبيه هية!)

Drugs that interfere with protein synthesis:
- Corticosteroids
- Tetracycline

In protein synthesis we have primary and secondary structure, so we can say tetra also 4

Hepatotoxcity

Covalent & Non-covalent bonds

Prof. Yieldes said:
Bonds for Reading only

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 : change in molecule itself

a type of chemical bond involving the sharing of electrons between atoms in a molecule (strong)
It is adduct formation between the metabolite of the drug & cellular macromolecules.

If covalent binding to protein → immunogenic reaction

If binding to DNA → carcinogenesis

Non-Covalent interactions : change in function

- Lipid peroxidation → generation of cytotoxic oxygen radicals.
- Impairment of mitochondrial respiration.
- Depletion of GSH reactions → 'oxidative stress'
- Modification of sulfhydryl groups → impair Ca2+homostasis
- Protein synthesis inhibition

.....etc

Hepatotoxins cause liver disease

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

- Environmental factors:

Race , Age , Sex , Nutritional status , Concomitant habits , drugs , diseases

- Host genetic makeup:

Metabolizing Enzymes , Detoxifying System , Drug Transport

Incidence of hepatotoxicity depends on:

- ❖ Toxicity potential
- ❖ Host genetic makeup
- ❖ Environmental Host factors

Those factors lead to:
Drug induced hepatotoxicity

Drug induced hepatic injury

Incidence of DIHI

Drugs produce about 10% of all cases of hepatitis in young adults and 40% of cases in patients older than 50 years.

Categories of people who are exposed to Hepatotoxins:

Tolerators	Adaptors	Susceptibles	In threat
No injury	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

presenting manifestations

Latency period:

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

- **In Direct dose-dependent Hepatotoxicity** → the Latency period is **SHORT** as it occurs after a threshold of toxicity is reached → acetaminophen
- **In Direct cumulative or In Indirect Immunoallergic Idiosyncratic Hepatotoxicity** → the Latency period is INTERMEDIATE , but may continue to evoke even after drug

Prof. Yieldez said it's NOT important

Histopathological finding

- No universal histo-pathological pattern of DIHI exist.

The commonest are : **Hepatocellular necrosis** , **Cholestasis** , **Steatosis**.

- More than one type of injury may occur in the same patient and Any one agent may produce different types of injury in different patients

Clinical pattern : Will be explained in the next slide

Drug induced hepatic injury

presenting manifestations

Clinical patterns

The clinical presentation could be of variable intensity ranging from asymptomatic ↑ of liver enzymes to Fulminant hepatic failure

it's important

ASYMPTOMATIC	SYMPTOMATIC MANIFESTATIONS		
increase In aminotransf -erases	injury targets **hepatocytes** Hepatocellular	If injury targets **biliary system** (canalicular or ductal) (CHOLESTASIS)	If injury targets both **hepatocytes & biliary system** (MIXED TYPE)
Examples Phenytoin Statins Sulfonamides Sulfonylureas	• apoptosis or necrosis (HEPATITIS)(cytotoxic) • **Symptoms**: develops rapid onset of malaise, severe anorexia(loss of appetite) and jaundice, Flu-like symptoms, muscle aches, weakness, GIT symptoms, diarrhea, urine discolored, Increase(3 fold) in alanine aminotransferases (**ALT**). Normal level of **ALP**.	• **Symptoms**: develop jaundice + severe pruritis predominate , dark urine, rash, stool may be light, hyperbilirubinaemia Normal level of **ALT** Increase(2 fold rise) in alkaline phosphatase(**ALP**)	• ALT: increase 3 folds • ALP: increase 2 folds
	• **Examples**: Acetaminophen (استنى أمين، فين هية ؟) NSAIDs (Hepa said that) Isoniazid (آذوا نياز وهية = Iso-niazid & Hepa) Amiodarone (أمي داريه عنك يا هية (Ami-o-darone)	• **Examples**: Chlorpropamide (Chole = Chlo) Erythromycin (كل الارث لنا = Chol eryth) Rifamycin (Chole ya rafeef) Oral contraceptives (كليه عن طريق الفم = Chole orally, no it is contraindicated) (ما يدري فين يشتغل ! على هذا أو ذاك) (سولفوا لي عن هذا و ذاك)	• **Examples:** Phenytoin Carbamazepine Sulfonamides ACE Inhibitors

Lines Of Treatment

1st step: Immediate withdrawal of any suspected drug.

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

Symptomatic:

- If a severe allergic reaction is observed (Corticosteroids)
- If pruritus → enhance bile acid excretion (**Cholestyramine**)
- If cholestatic liver injury **Ursodeoxycholic acid** (Ursodiol)
- If coagulopathy or encephalopathy develop → treat accordingly

Supportive:

High carbohydrate, moderate protein and fat diet adequate in calories

Specific antidotes :

- For Acetaminophen toxicity → **N-acetylcysteine**
- For Valproate toxicity → **L-carnitine**

For Drug induced Fulminant Hepatic failure

↓

Emergency liver transplantation

Cases- From doctor's slides

Case 1

A long standing rheumatoid arthritic patient developed TB 2 months ago. Today she was received in the ER complaining of yellowish discoloration, 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 months ago on cyclosporine to control the arthritic exacerbations. A month ago, she was put on isoniazid when she developed TB and multivitamins because she is weak. Currently she is given domperidone for the emesis. Lab results reveals severe elevation in ALT but no elevation on ALP.

Q1: Which one of the following drugs is the likely cause of her symptoms?

A. Cyclosporine
B. Multivitamins
C. Isoniazid
D. Domperidone

Q2: Which type of Hepatotoxin is considered? Immunoallergic Idiosyncrotic

Q3: What is the likely hepatotoxic pattern inflicted by the drug?

Hepatocellular / Hepatitis-like pattern

Case 2

A hypercholesterolemic patient was received in the ER complaining of yellowish discoloration of the skin, change in the color of the urine & stools, and severe itching. He has been receiving statins for the long time for the hypercholestrolemia. 3 months 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 has a flue for which he was given acetaminophen for muscle aches and nasal drops for his nasal stuffiness. Lab investigation shows severe elevation of ALP and no significant elevation in ALT

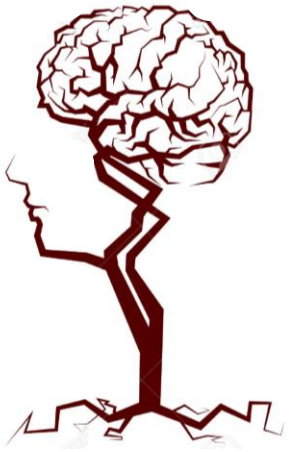
Q1: Which one of the following drugs is the likely cause of his symptoms?

A. Nadolol
B. Chlorpropamide
C. Acetaminophen
D. Statins

Q2: Which type of Hepatotoxin is considered? Immunoallergic Idiosyncrotic

Q3: What is the likely hepatotoxic pattern inflicted by the drug?

Cholestasis / Inflammatory cholestasis



إِنَّ فِي ذَٰلِكَ لَآيَاتٍ لِّقَوْمٍ يَتَفَكَّرُونَ ﴿٣﴾

قادة فريق علم الأدوية :

- جومانا القحطاني - اللولو الصليهم
- فارس النفيسة

الشكر موصول لأعضاء الفريق المتميزين :

روان القحطاني
ليلى المذكور
أنوار العجمي
دعاء وليد

References :
1- 436 Prof. Yieldez slides and notes
2- male's notes