Lecture 7

HEPATOTOXIC DRUGS

Learning 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

Additional Notes

Explanation –Extra-

Important

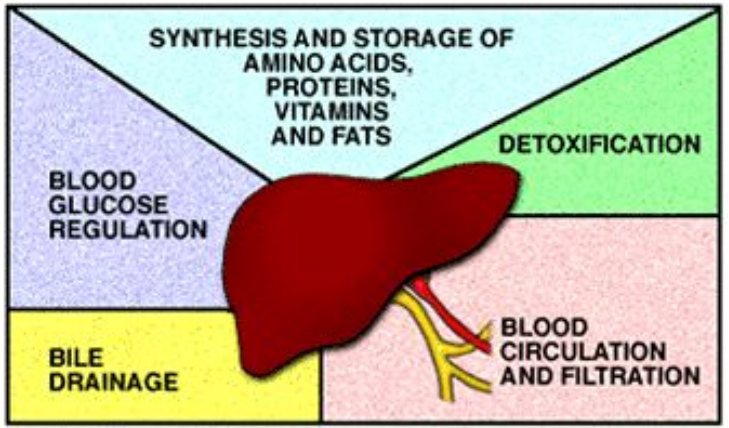
before starting, please check our GIT block correction

For any correction, suggestion or any useful information
do not hesitate to contact us: Pharmacology434@gmail.com

Functions Of The Liver

Regulation, synthesis & secretion	Storage	Purification, transformation & clearance
• utilization of glucose, lipids & proteins + bile to digest fats.	• Glucose (as glycogen • fat soluble vitamins (A, D, E & K) • minerals	• Endogenous: steroidal hormones, cholesterol, FA, & proteins • exogenous :drugs, toxins, herbs and chemicals.

- Human body identifies almost all drugs as foreign substances i.e. XENOBIOTIC
- So it has to get rid of these metabolic substances
- The liver is :METABOLIC CLEARING HOUSE



LIVER FUNCTIONS

Metabolic Function Of The Liver

In the liver drugs are subjected to chemical transformation (metabolism)

The aim of metabolic processes is to inactivate the drug and enhance its execration

Enhancement of execration: by changing the formula of a drug from lipophilic (most drugs are lipophilic) to Hydrophilic water soluble drugs which are easily execrated through the bile or urine

Metabolic transformation

PHASE1 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

PHASE2 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**: it Is the Leading cause of ADRs.
- **Drug Induced Liver Injury:**
- Caused by exposure to a drug
- Injury / damage of the liver (Inflammation ⇨Apoptosis ⇨ Necrosis)
- Inflict varying impairment in liver functions

- Manifests clinically a long range ➔ hepatitis ⇨failure

- 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

Why The Liver Is The Major Site Of ADRs ?

Drug (Pro-toxin)	enzyme	Toxin		Injury
Paracetamol	CYT: P450	NABQI*		Centrilobular liver necrosis

(NAPBQI) : N-acetyl-p-benzoquinone imine

Toxicity Potential Of The Drug, either by:

- Chemical composition of the drug itself
- Conjugation reactions linked to it & their availability
- Nature of its reactive metabolite
- Mitochondrial effects of the drug
- Drug formulation (Long-acting drugs)

HEPATOTOXIC DRUGS

- HEPATOTOXIN **:** are Drugs that can cause ADRs in the liver (hepatotoxicity)
- Note that not all drugs cause liver related ADRs (hepatotoxicity). it depends on "Toxicity Potential Of The Drug" it self.

Hepatotoxic Drug	Dose	Hepatotoxicity	ADRs
intrinsic hepatotoxin	Supertherapeutic* or cumulative dose*	1- direct hepatotoxicity	type A ADRs: predictable / direct
idiosyncratic hepatotoxin	normal dose	2- indirect hepatotoxicity	type B ADRs: unpredictable / bizzar / idiosyncratic

* Super-therapeutic dose: the toxicity is related to overdose.
* cumulative dose: the toxicity is related to repeated admiration of the drug.

1-DIRECT HEPATOTOXICITY

- **Type A: Dose-dependent hepatotoxicity**
  - **Caused by intrinsic hepatotoxin.**

Increased Dose	Cumulative Dose/effect	BOTH
• Acetaminophen • paracetamol • Salicylates • Statins(Hyperlipidemia)	• Amiodarone • Oral contraceptives	• Methotrexate • anticancer • Alcohol

2-INDIRECT HEPATOTOXICITY

INDIRECT HEPATOTOXICITY

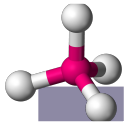
- Type B: Dose-independent hepatotoxicity
- Caused by idiosyncratic hepatotoxin.

a-Hypersensitivity or immunoallergic reactions		b-Metabolic-idiosyncratic reactions	
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	
Inflammatory cholestasis	**Viral hepatitis-like pattern**	**Interfere with bilirubin metabolism**	**Interfere with protein synthesis**
Chlorpromazine. antipsychotic Chlorpropamide. Oral hypoglycemic Erythromycin.	Isoniazid. TB Phenytoin. antiepileptic Methyldopa. Parkinson	Erythromycin Rifampicin	Corticosteroids Tetracycline

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

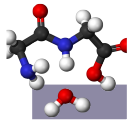
HOW CAN A DRUG INDUCED HEPATOTOXICITY ?!

- A Drug or its reactive metabolites can form <u>covalent bonds</u> with target molecules or alter the target molecule by <u>non-covalent interactions</u> (weaker) or both



COVALENT INTERACTIONS

- a type of chemical bond involvin g 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

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

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

ENVIRONMENTAL	HOST
HOST FACTORS	GENETIC MAKEUP
Race / Age / Sex /	Metabolizing Enzymes
Nutritional status	Detoxifying System
Concomitant habits /	Drug Transport
drugs / diseases	

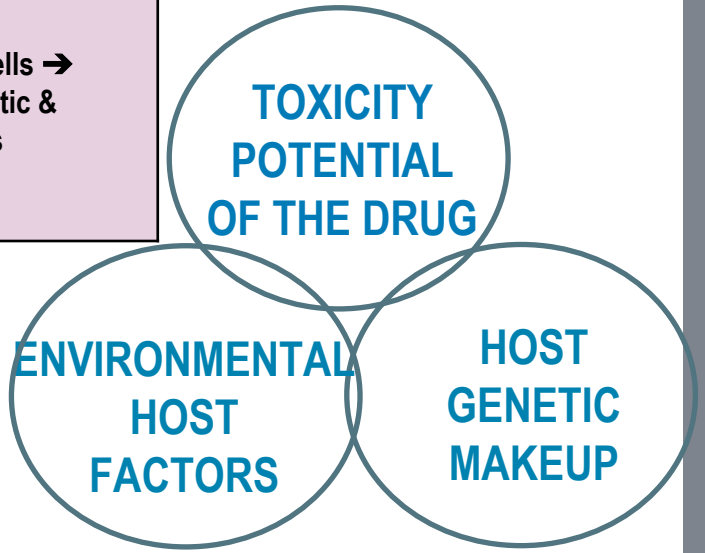
DRUG-INDUCED HEPATIC INJURY

in young adults = 10% of the cases of hepatitis
older than 50 years = 40% of the cases

(because of the decrees in liver function with aging)

Upon exposure to hepatotoxins people are categorized :

Tolerators	Adaptors	Susceptibles	In Threat
➔ No injury.	➔Mild transient injury but adapt.	➔Develop symptoms (depending on existing predisposing factors)	:➔devolve HEPATIC INJURY➔ due loss of synthetic & clearance function with recruitment of inflammatory cells ➔ provoke apoptotic & necrotic signals



What are the presenting manifestations?

Each drug has CHARACTERISTIC SIGNATURE → composed of:

A particular latency period			A clinical pattern	A particular pathological finding
short (hrs/dys)	intermediate (1-8ws)	long (1-12ms)		
In Direct dose-dependent Hepatotoxicity → Latency period → SHORT as it occurs after a threshold of toxicity is reached → *acetaminophen* (toxic dose)	In Direct cumulative or In Indirect Immunoallergic Idiosyncratic Hepatotoxicity → Latency period → INTERMEDIATE → but may continue to evoke even after drug			

CLINICAL PATTERNS

Drugs inducing **ASYMPTOMATIC MANIFESTATIONS**		Drugs inducing **SYMPTOMATIC MANIFESTATIONS**		
Cause increase in liver enzymes		**Hepatic injury**		
increase In aminotransferases.		**Hepatocellular injury** ➔ targets hepatocytes ➔ apoptosis or necrosis ➔ **HEPATITIS** (cytotoxic) develops ➔ rapid onset of malaise, severe anorexia and jaundice + increase in alanine aminotransferases (ALT)	**Cholestatic injury** ➔ targets biliary system (canalicular or ductal) ➔ **CHOLESTASIS** develop ➔ jaundice + severe pruritis predominate > increase in alkaline phosphatase (ALP) + hyperbilirubinaemia	**Mixed injury** ➔ targets both hepatocytes & biliary system ➔ **MIXED TYPE**
		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
• Phenytoin • Statins • Sulfonamides		• Acetaminophen • NSAIDs • Isoniazid • Amiodarone	• Chlorpropamide • Erythromycin • Rifamycin • Oral contraceptives	• Phenytoin • Carbamazepine • Sulfonamides • ACE Inhibitors

lines of treatment

Immediate withdrawal	*No specific treatment*	*Specific antidotes*	*Emergency liver transplantation*
of any suspected drug	Symptomatic *treatment :* • *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 *treatment* High carbohydrate, moderate protein diet adequate in calories	N-acetylcysteine ➔ for acetaminophen toxicity L-carnitine ➔for valproate toxicity	for drug induced fulminant hepatic failure

SCENARIOs

Cholestatic

A hypercholestrolemic patient was received in E.R complaining of yellowish discoloration of skin (jaundice) change in color of urine & stools, and severe itching He has been receiving :

- statins for the long time for the hypercholestrolemia. Three month ago he was diagnosed as being diabetic and hypertensive and since then he is receiving chlorpropamide for the diabetes nadolol for the hypertension.

The last couple of days he had a flue; for which he was given acetaminophen 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. Acetaminophen d. Statins

Which type of hepatotoxin it is considered? Immunoallergic Idiosyncratic Hepatotoxicity (indirect)

What is the hepatotoxic pattern inflicted by the drug? Inflammatory cholestasis

SCENARIOs Hepatocellular

A long standing rheumatoid arthritic patient developed tuberculosis 2 month ago. Today she was received in E.R complaining 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, 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? Immunoallergic Idiosyncratic Hepatotoxicity (indirect)

What is the likely hepatotoxic pattern inflicted by the drug?
Viral hepatitis-like pattern

Good luck!

Done by Pharmacology team

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For any correction, suggestion or any useful information do not hesitate to contact us: Pharmacology434@gmail.com