HEPATOTOXIC DRUGS

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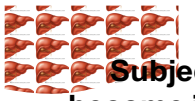
- هذي النوتز عبارة عن **المهم والمطلوب في الامتحان** ،، اللي حاب يفهم أكثر يرجع للسلايد .



HEPATOTOXIC DRUGS

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

Such metabolic transformation usually occur in 2 PHASES:

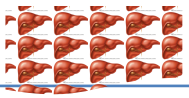
Phase 1 reactions
Oxidation, Reduction, Hydrolysis, Hydration
Catalyzed by CYT P-450

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



HEPATOTOXIC DRUGS

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)	enzyme	Toxin	The affected part of liver	Injury
Paracetamol	→ *CYT P450* →	NAPBQI		centrilobular
Allyl alcohol	→ *alcDH* →	acrolein		periportal

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

Drugs that can cause ADRs in the liver (hepatotoxicity) are called → HEPATOXIN

Types of drug-induced hepatotoxic ADRs (hepatotoxin)	**INTRINSIC HEPATOTOXIN** (they are related to Supertherapeutic or cumulative dose of the drug)	**IDIOSYNCRTIC HEPATOTOXIN** (they are related to normal dose of the drug)
type of hepatotoxicity	**Type A : DIRECT HEPATOTOXICITY** (*Dose-dependent hepatotoxicity)*	**Type B : INDIRECT HEPATOTOXICITY** (*Dose-independent hepatotoxicity)*
TYPE of ADRs	PREDICTABLE / DIRECT	UNPREDICTABLE / BIZZAR / IDIOSYNCRATIC
Divided into	**- Direct increased dose dependent hepatotoxicity:** *Acetaminophen *Salicylates *Statins **- Direct cumulative hepatotoxicity :** *Amiodarone *Methotrexate (Also has increased dose dependent) *Oral contraceptives	**- Hypersensitivity or immunoallergic reactions :** A drug or its metabolite binds to hepatic membranes or proteins ➔act as hapten to induce a variety of immune reactions **Divided into:** **1- Inflammatory cholestasis** Chlorpromazine. Chlorpropamide. Erythromycin. **2- Viral hepatitis-like pattern** Halothane. Isoniazid. Phenytoin. Valproic acid. Methyldopa. **- Metabolic Idiosyncratic Hepatotoxicity :** The metabolite of the offending drug interferes with hepatic metabolism as that of bilirubin or protein synthesis….etc **Divided into:** **1- Interfere with bilirubin metabolism** Chlorpromazine Estrogen & Androgen Erythromycin Rifampicin **2- Interfere with protein synthesis** Corticosteroids Tetracycline

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

This is an imp. Note which must be known >> to prevent any confusion about those drugs which are repeated .

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

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
…..etc

What are the presenting manifestations?

Individual drugs tend to have CHARACTERISTIC SIGNATURE composed of: latency period , clinical pattern & pathological pattern

Imp. !!

LATENCY PERIOD

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

Direct Hepatotoxicity

short Latency period

e.g. *acetominophen* (toxic dose) /*amiodarone* (cumulative doses)

Indirect Immunoallergic Idiosyncratic Hepatotoxicity

intermediate Latency period

e.g. phenytoin, sulfa drugs, halothane

!! but may continue to evoke even after drug withdrawal

Indirect Metabolic Idiosyncrotic Hepatotoxicity

usually long ➔ Unpredictable ➔ most problematic

e.g. *Isoniazid, tetracyclines, chlorpromazine*

CLINICAL PATTERNS

The clinical presentation could be of variable intensity, ranging from asymptomatic ↑of liver enzymes → → → fulminant hepatic failure

ASYMPTOMATIC

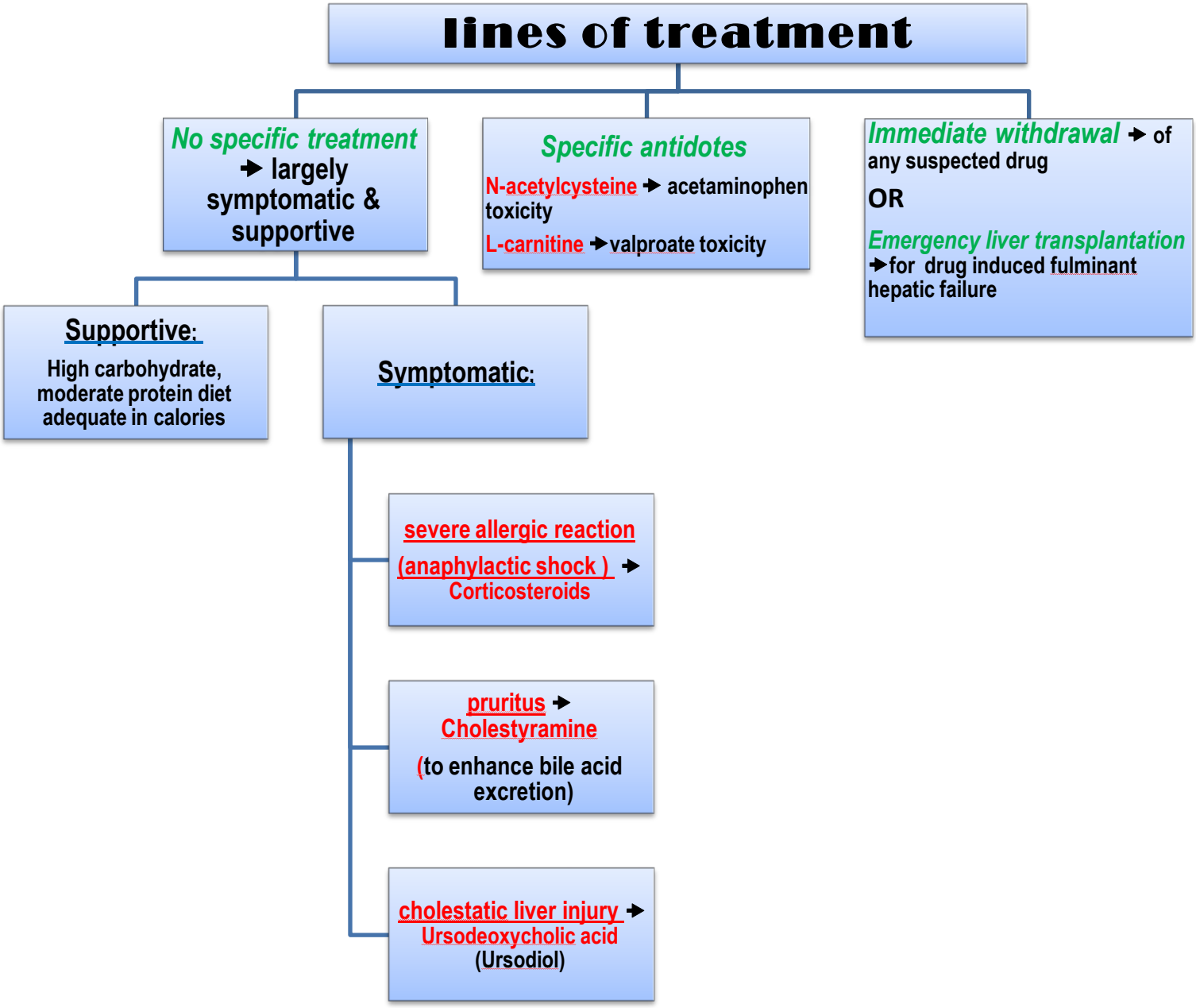
(↑ IN AMINOTRANSFERASES)

e.g. Methyldopa , Phenytoin, Statins , Sulfonamides , Salicylates , Sulfonylureas , Quinidine

SYMPTOMATIC MANIFESTATIONS

(see the table below)

Some PATTERNS of SYMPTOMATIC drug-induced liver disease			
Hepatic injury	**Hepatocellular** (hepatocytes)	**Cholestatic** (biliary system (canalicular or ductal)	**Mixed** (hepatocytes & biliary system)
	Flu-like, malaise, m. aches weakness, loss of appetite (anorexia), GIT symptoms, diarrhea, jaundice, urine discolored	Yellowish discoloration of skin(jaundice), dark urine, rash, pruritus (itching), stool may be light, hyperbilirubinaemia	
ALT	≥ 3 fold rise	Normal or slight	≥ 3 fold rise
ALP	Normal	≥ 2 fold rise	≥ 2 fold rise
Examples	↓ Acetaminophen ↓ Salicylates & NSAIDs ↓ Isoniazid ↓ a-methyldopa ↓ Griseofulvin ↓ Azoles; Fluconazole ↓ Amiodarone	↓ Chlorpromazine ↓ Chlorpropamide ↓ Erythromycin ↓ Rifamycin ↓ Cimetidine ↓ Anabolic steroids ↓ Oral contraceptives	↓ Phenytoin ↓ Carbamazepine ↓ Sulfonamides ↓ ACE Inhibitors ↓ TCAs; Amitryptyline


lines of treatment
No specific treatment ➔ largely symptomatic & supportive
Specific antidotes
N-acetylcysteine ➔ acetaminophen toxicity
L-carnitine ➔ valproate toxicity
Immediate withdrawal ➔ of any suspected drug
OR
Emergency liver transplantation ➔ for drug induced fulminant hepatic failure
Supportive:
High carbohydrate, moderate protein diet adequate in calories
Symptomatic:
severe allergic reaction (anaphylactic shock) ➔ Corticosteroids
pruritus ➔ Cholestyramine
(to enhance bile acid excretion)
cholestatic liver injury ➔ Ursodeoxycholic acid (Ursodiol)

A long standing rheumatoid arthritic 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, 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 .

hepatocellular

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

  a.Cyclosporine b. Multivitamines c. Isoniazid d.Domperidone
- Which type of hepatotoxin it is considered?

  IDIOSYNCRTIC HEPATOTOXIN
- What is the likely hepatotoxic pattern inflicted by the drug?

  INDIRECT HEPATOTOXICITY (Indirect Immunoallergic Idiosyncratic Hepatotoxicity)
- Treatment???? No treatment - (treatment only for cases are included within the lines of treatment that mentioned before)

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 .

Cholestatic

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

  a. Nadolol b. Chlorpropamide c. Acetominophen d. Statins
- Which type of hepatotoxin it is considered?

  IDIOSYNCRTIC HEPATOTOXIN
- What is the hepatotoxic pattern inflicted by the drug?

  INDIRECT HEPATOTOXICITY (indirect Immunoallergic Idiosyncratic Hepatotoxicity)

Treatment????

يعتمد على المطلوب في السؤال لو طلب:

- **Treatment of pruritus >> Cholestyramine**
- **Treatment of cholestatic liver injury ➔ Ursodeoxycholic acid (Ursodiol)**