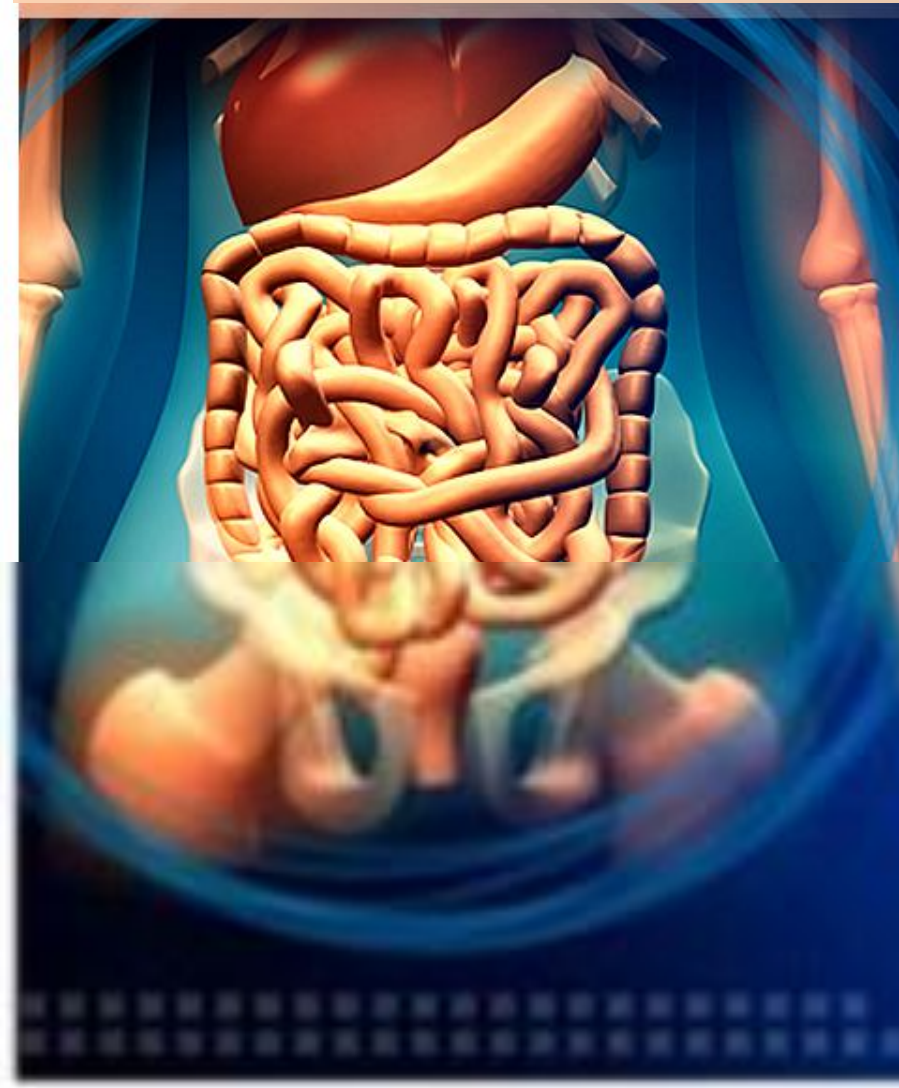
King Saud University
College of Medicine
2nd Year, 2nd Block

GIT BLOCK

PHARMACOLOGY 433

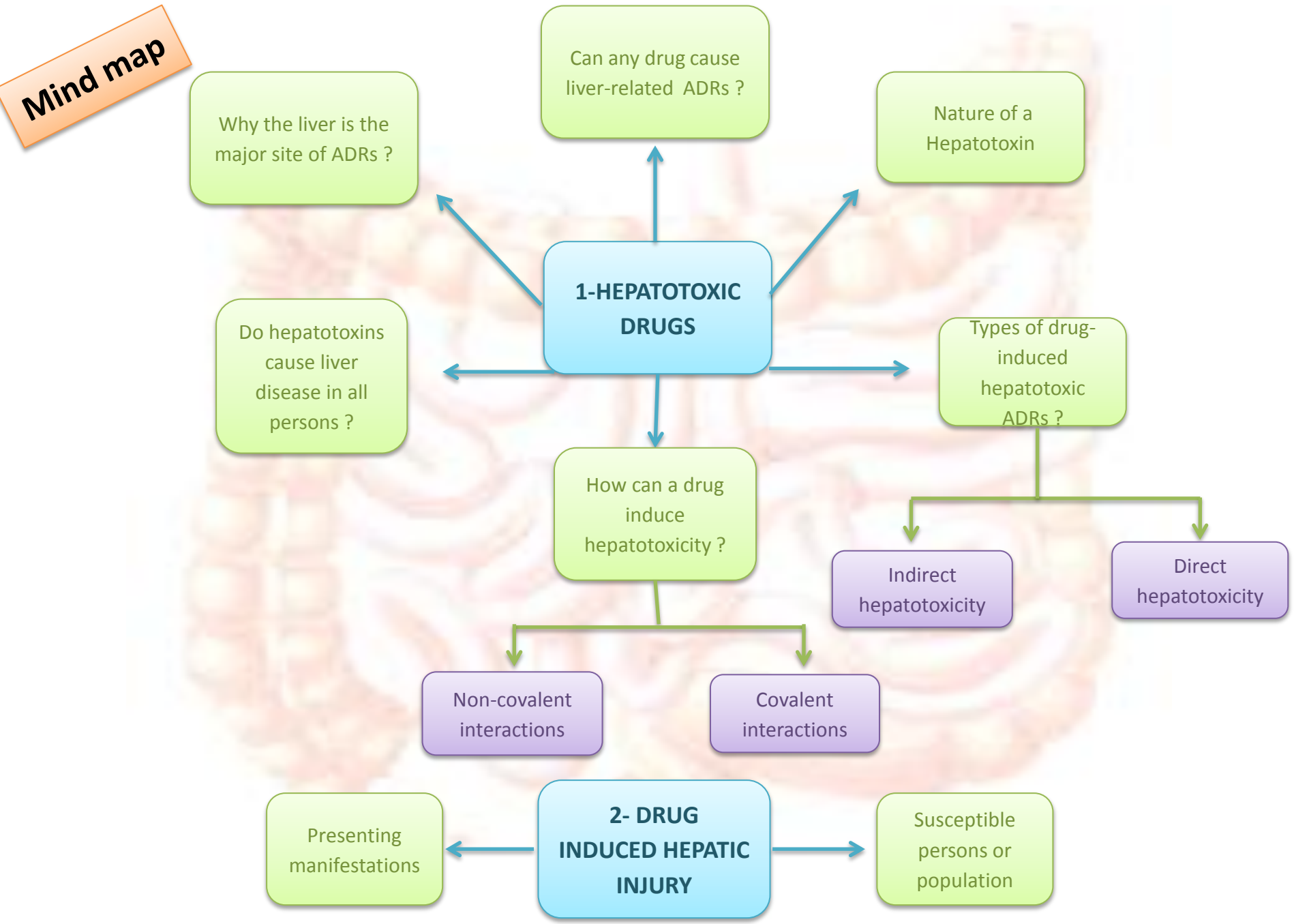
MED 433 Teams



Lecture 7: hepatotoxic drugs

Learning Objective

- ✓ **Clarify the role of liver in drug detoxification**
- ✓ **Elaborate types (patterns) of hepatotoxicity**
- ✓ **Classify hepatotoxins**
- ✓ **Explain how a drug can inflict hepatotoxicity**
- ✓ **State the pathological consequences of hepatic injury**
- ✓ **Contrast the varied clinical presentation of hepatotoxicity**
- ✓ **Enlist the possible treatment**



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Introduction

- Liver has multiple functions >5000
- liver is called METABOLIC CLEARING HOUSE

- Liver and drugs :

- Since most drugs are lipophilic ➔ they are changed into hydrophilic water soluble products ➔ suitable for elimination through the bile or urine.
- So drugs need to chemical transformation (METABOLISM) ➔ to become inactive & easily excreted.

- Metabolism of the drugs :

Mostly happen in the liver in two phases :

- Phase 1 reactions (modification) : for not polar drugs
- Oxidation, Reduction, Hydrolysis, Hydration or Catalyzed by CYT P-450.
- Result: polar, transient, usually highly reactive or more toxic than parent substrates which may result in liver injury

- Phase 2 reactions Conjugation with a moiety : toxic drugs tend to have this reaction
- moiety like acetate, a.a., glutathione, glucuronic a., sulfate.
- Result : Yields products of increased solubility
  If of high molecular weight → excreted in bile
  If of low molecular weight → to blood → excreted in urine

Classification of the bad effects of drugs :

1- HEPATOTOXIC DRUGS	2- DRUG INDUCED LIVER INJURY
Is the Leading cause of ADRs	Inflammation ⇨Apoptosis ⇨ Necrosis

1- HEPATOTOXIC DRUGS

- Not all drugs cause ADRS.
- The major site of ADRs is liver because ?

- 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

e.x. Paracetamol →CYT P450 → NABQI centrilobular necrosis

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

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IMPORTANT

1- HEPATOTOXIC DRUGS depends on

1. Nature of a Hepatotoxin

- 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

2.Types of drug-induced hepatotoxic ADRs it inflicts تلحق

2.1-intrinsic hepatotoxin		2.2-idiosyncratic hepatotoxin*next slide*
Direct		Indirect
Predictable		Unpredictable / bizzar
-SUPERTHERAPEUTIC - or CUMULATIVE dose		-NORMAL dose
Statins Acetaminophen	- Superthera peutic *Increased Dose*	A- Hypersensitivity or immunoallergic reactions
Oral contraceptives Amiodarone	Cumulative Dose	B- Metabolic-idiosyncratic reactions

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IMPORTANT

2.2- IDIOSYNCRATIC HEPATOTOXIN

A. Immunoallergic Idiosyncratic Hepatotoxicity		B. Metabolic Idiosyncratic Hepatotoxicity	
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	
Viral hepatitis-like pattern	Inflammatory cholestasis	Interfere with bilirubin metabolism	Interfere with protein synthesis
❖ Isoniazid. ❖ Phenytoin. ❖ Methyldopa.	❖ Chlorpromazine. ❖ Chlorpropamide. ❖ Erythromycin.	❖ Erythromycin ❖ Rifampicin	❖ Corticosteroids ❖ Tetracycline

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

يمكن أن يكون أكثر من خاصيه للدواء كما خُط بالأحمر

HOW CAN A DRUG INDUCE HEPATOTOXICITY ?

by covalent bonds with target molecules or alter the target molecule 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

DO HEPATOTOXINS CAUSE LIVER DISEASE IN ALL PERSONS ?

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

1-ENVIRONMENTAL HOST FACTORS

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

2-HOST GENETIC MAKEUP

Metabolizing Enzymes/ Detoxifying System / Drug Transport

2- DRUG INDUCED LIVER INJURY

IMPORTANT

- **Injury / damage of the liver ➔ <u>Caused by exposure to a drug</u> ➔ Inflict varying impairment in liver functions ➔ Manifests clinically a long range ➔ hepatitis ⇨failure**

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

Upon exposure to hepatotoxins people are categorized as:	
Tolerators	No injury
Adaptors	Mild transient injury but adapt
Susceptibles	Develop overt symptoms depending on existing predisposing factors
Threat	DILI accelerates beyond initial targets due to ➔loss of synthetic & clearance function of hepatocyte with recruitment of inflammatory cells provoke apoptotic & necrotic signals

DEPEND ON ?

1-Toxicity Potential Of the drug

2- Host Genetic Makeup

3-Environmental Host Factors

EACH Individual drugs tend to HAVE ?

1-A particular latency period

2-A clinical pattern

IMPORTANT

1-latency period

latency period	categories	Drug like
SHORT Hours - Days	**Direct** dose-dependent	**1-acetaminophen**
INTERMEDIATE 1 Weeks – 8 Weeks	**Direct** dose-dependent	**1-amiodarone** **"cumulative"** **2-phenytoin, isoniazid** **"Idiosyncratic"**
LONG 1 month – 12 months	**Indirect** Metabolic Idiosyncratic	**1-tetracyclines,** **2-oral contraceptives**

2-A clinical pattern

A-ASYMPTOMATIC "↑ In aminotransferases"	B-SYMPTOMATIC *next slide*
Phenytoin	Acetaminophen +NSAIDs +Isoniazid +Amiodarone **((Hepatocellular type))**
Statins	Chlorpropamide +Erythromycin +Rifamycin +Oral contraceptives **((Cholestatic type))**
Sulfonamides	Phenytoin +Carbamazepine +Sulfonamides +ACE Inhibitors **((Mixed injury))**
Sulfonylureas	

IMPORTANT

B-SYMPTOMATIC DRUG INDUCED LIVER DISEASE

HEPATIC INJURY	MANIFESTATION		DRUGS LIKE
Hepatitis = Means the injury targets hepatocytes	**Flu-like, malaise**, muscle aches weakness, **loss of appetite**, GIT symptoms, diarrhea, jaundice, urine discolored, **severe anorexia**	↑ in alanine aminotransferases (ALT) while ALP Normal	Acetaminophen +NSAIDs +Isoniazid +Amiodarone
Cholestitis = Means the injury targets biliary system	jaundice, dark urine, rash, **pruritus**, stool may be light	↑ in alkaline phosphatase (ALP) ± hyperbilirubinaemia While ALT Normal or slight high	Chlorpropamide +Erythromycin +Rifamycin +Oral contraceptives
Mixed = Means the injury targets both	_____	Both are rise ,but ALT much higher	Phenytoin +Carbamazepine +Sulfonamides +ACE Inhibitors

slide doctor's note important explanation

IMPORTANT

Lines of treatment

1)Immediate withdrawal	2)Symptomatic	3)Specific antidotes	4)Emergency liver transplantation
of any suspected drug (If it cause an injury u immediately stop it)	**1-**severe allergic reaction **USE** Corticosteroids **2-** pruritus **USE** Cholestyramine **3-** cholestatic liver injury **USE** Ursodeoxycholic acid (Ursodiol) **4-**coagulopathy or encephalopathy develop **USE** High carbohydrate, moderate protein diet	1-acetaminophen toxicity **use** N-acetylcysteine (if a child took overdose or someone commit suicide) 2-valproate toxicity **use** L-carnitine	FOR Drug induced fulminant hepatic failure

* Scenario will be given and u will be asked about the treatment

IMPORTANT

SCENARIO

1
Cholestatic

A hypercholestrolemic patient was received in E.R complaining of yellowish discoloration of skin, change in color of urine & stools, and **severe itching** (pruritus)

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

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

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

We exclude

***statin** because its not associated with cholestasis

* **acetaminophen** associated with short latency and supertherapeutic dose

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.

2
Hepatocellular

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

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Summary

Drug	Type	Sub-type	Latency period	Hepatic injury
Acetaminophen	Intrinsic	Supertherapeutic	Short	Hepatocellular
Statin	Intrinsic	Supertherapeutic	Short	-
Amiodarone	Intrinsic	Cumulative	Intermediate	Hepatocellular
Oral contraceptive	Intrinsic	Cumulative	Long	Cholestatic
Isoniazid	Idiosyncratic	Immunoallergic	Intermediate	Hepatocellular
Phenytoin	Idiosyncratic	Immunoallergic	Intermediate	Mixed
Methyldopa	Idiosyncratic	Immunoallergic	Intermediate	Hepatocellular
chlorpromazine	Idiosyncratic	Immunoallergic	Intermediate	Cholestatic
chlorpropamide	Idiosyncratic	Immunoallergic	Intermediate	Cholestatic
Erythromycin	Idiosyncratic	Immunoallergic and metabolic	Intermediate	Cholestatic
Rifampicin	Idiosyncratic	metabolic	Long	Cholestatic
Corticosteroids	Idiosyncratic	metabolic	Long	-
Tetracycline	Idiosyncratic	metabolic	Long	-

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Quiz yourself

answers 1-D 2-B 3-A 4-D 5-A 6-A 7-B 8-A 9-B

1- Patient is taking drug A, after one month from taking this drug he developed flu-like malaise, what is drug A?

A- Tetracycline
B- Acetaminophen
C- Erythromycin
D- Isoniazid

2- According to Q1, which type of hepatotoxin is considered?

A- intrinsic cumulative
B- Immunoallergic Idiosyncratic
C- metabolic idiosyncratic
D- Intrinsic Supertherapeutic

3- A patient took an increased dose of drug B, after one hour he developed anorexia and muscle aches, what is drug B?

A- Acetaminophen
B- Rifampicin
C- Phnytoin
D- Corticosteroids

4- According to Q3, which type of hepatotoxin is considered?

A- intrinsic cumulative
B- Immunoallergic Idiosyncratic
C- metabolic idiosyncratic
D- Intrinsic Supertherapeutic

5- According to Q3, what is the treatment?

A- N-acetylcysteine
B- Cholestyramine
C- L-carnitine
D- Corticosteroids

6- Which of these drugs is a metabolic idiosyncratic and interferes with protein synthesis?

A- Tetracycline
B- Rifampicin
C- Erythromycin
D- chlorpromazine

7- Patient is taking drug A, after 6 months from taking this drug he developed pruritus, what is drug A?

A- Amiodarone
B- Oral contraceptives
C- Phnytoin
D- Statin

8-According to Q7, which type of hepatotoxin is considered?

A- intrinsic cumulative
B- Immunoallergic Idiosyncratic
C- metabolic idiosyncratic
D- Intrinsic Supertherapeutic

9- According to Q7, what is the treatment?

A- N-acetylcysteine
B- Cholestyramine
C- L-carnitine
D- Corticosteroids

Done by

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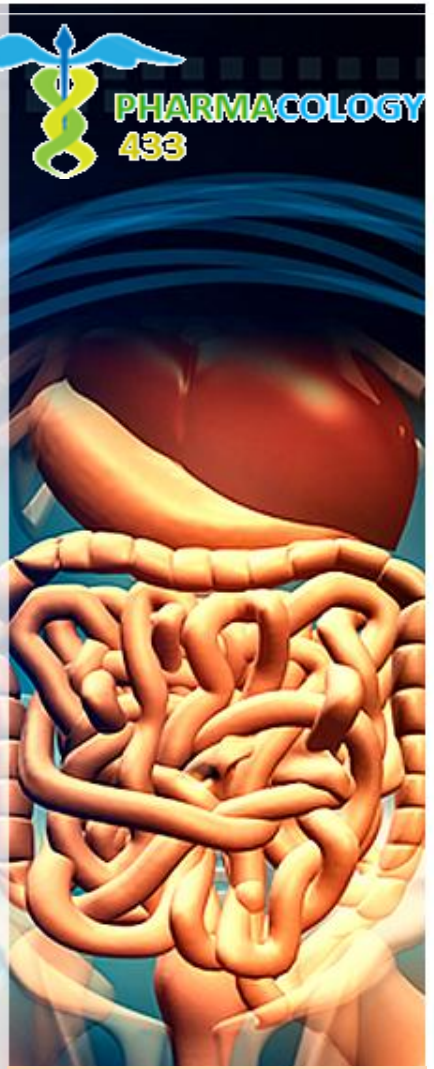
It always seems impossible until it is done

BEST OF LUCK



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