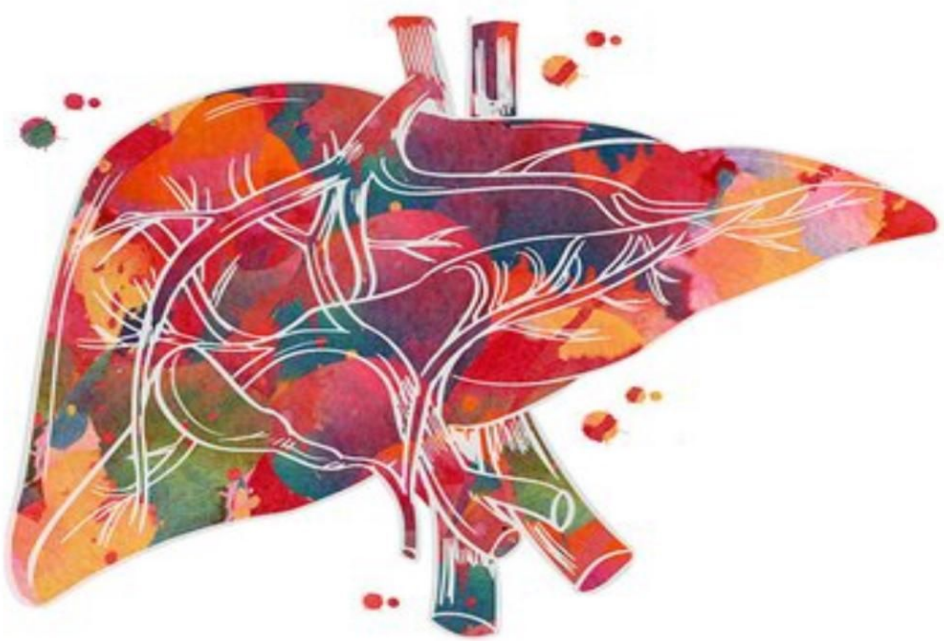
Pharmacology
Team 437

MED437
KING SAUD UNIVERSITY



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

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Editing File

Color index: Important Note Extra

Mind Map

Metabolic **functions** of the liver

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

The aim of the metabolic process is to **inactivate** the drug and **enhance its excretion**

Enhancement of excretion: by **changing the formula** of the drug from lipophilic (most drugs are lipophilic) to hydrophilic water soluble drugs the are easily excreted through the bile or urine

Metabolic **transformation**

Phase 1:
Oxidation,reduction,hydrolysis,hydration, catalysed by p450

Phase 2:
Conjugation with a moiety (acetate, A.A, glutathione, glucuronic acid , sulfate)

Hepatotoxic drugs

Direct (Intrinsic Hepatotoxin)	**Indirect** (Idiosyncratic Hepatotoxin)
Supratherapeutic or cumulative dose	Normal dose
Type A ADRs: Predictable, direct	Type B ADRs:Unpredictable/ Idiosyncratic/ Bizaar

Physiological

They won't ask about this slide

Liver has multiple functions (>5000) ➔ can be categorized into:

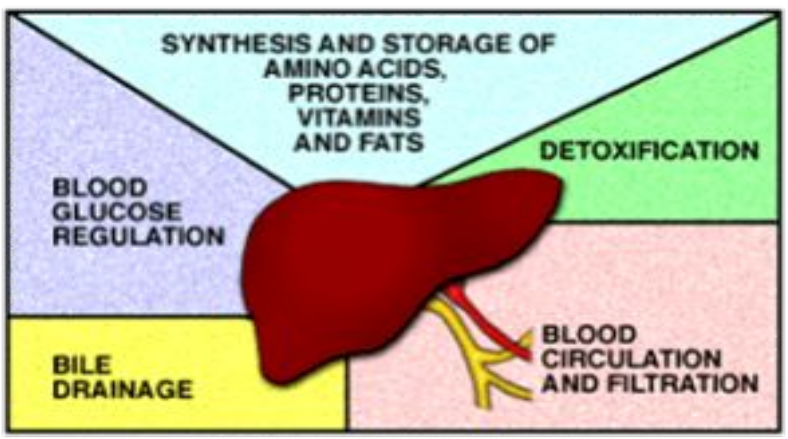
Regulation, synthesis & secretion	→	Utilization of glucose, lipids & proteins + bile for digesting fats
Storage	→	Glucose (as glycogen), fat soluble vitamins (A,D,E,K) & minerals
Purification, transformation & clearance	→	**Of endogenous (steroid hormones, cholesterol, FA, & proteins) & exogenous (drugs, toxins, herbs) 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

Metabolism of drugs in the liver

•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 <u>2 phases</u>:

Phase 1 reactions	Phase 2 reactions
Oxidation, Reduction, Hydrolysis, Hydration Catalyzed by **CYT P-450**	**Conjugation** with a moiety (acetate, a.a., glutathione, Glucuronic a., sulfate)
Yields intermediates → polar, transient, usually highly reactive far **more toxic than parent substrates** → may result in liver injury Drug-Induced Liver Injury (DILI)	Yields products of increased solubility • If of high molecular weight → excreted in bile. • If of low molecular weight → to blood → excreted in urine.

•Hepatotoxicity is 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

Hepatotoxic Drugs

Why the live 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

Just Read it

- Not all drugs do so
- Drugs that can cause ADRs in the liver (hepatotoxicity) are called HEPATOTOXIN

Toxicity potential of the drug

Just Read it

•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).

Types of drug-induced hepatotoxic

intrinsic hepatotoxin

Direct hepatotoxicity.
Inflicted by:

1. Super-therapeutic
   the toxicity is related to overdose.
2. Cumulative
   the toxicity is related to repeated doses of the drug.

belong to type A ADRS : **predictable** / direct.

type A ADRS: drug side effect which is predictable. E.g.: warfarin may cause bleeding in large dose.
Related to pharmacological effect.

idiosyncratic hepatotoxin

Indirect hepatotoxicity
Inflicted by: Normal dose.

Belong to type B ADRS: **bizarre / unpredictable / idiosyncratic** .

type B ADRS: unpredictable side effect, may happened because of hypersensitivity. e.g. chlorpromazine, it SMTM causes cholestatic jaundice. Don't related to pharmacological actions

DIRECT hepatotoxicity

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

Cumulative Dose/effect = for long time	- Amiodarone. Antiarrhythmic - Oral contraceptives
Increased Dose	- Acetaminophen (Paracetamol) - Salicylates (both NSAIDs) - Statins. (Hyperlipidemia)
BOTH	- Methotrexate. anticancer - Alcohol

INDIRECT hepatotoxicity

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

Hypersensitivity(immuno-allergic reactions)

A drug or its metabolite binds to hepatic membranes or proteins which act as hapten to induce a variety of immune reactions.

Inflammatory cholestasis	Viral hepatitis-like pattern
• Chlorpromazine antipsychotic • Chlorpropamide Oral hypoglycemic for DM • **Erythromycin**	• **Isoniazid**. TB • Phenytoin. Antiepileptic • Methyldopa. Parkinson

Metabolic-idiosyncratic reactions

The metabolite of the offending drug interferes with hepatic metabolism as that of bilirubin or protein synthesis…etc

Interfere with bilirubin metabolism	Interfere with protein synthesis
• Erythromycin • Rifampicin	• Corticosteroids • Tetracycline

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

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:	Non-covalent interactions
A type of chemical bond involving the sharing of electrons between atoms in a molecule **(stronger)**. • It is adduct formation between the metabolite of the drug and cellular macromolecules • If covalent binding **to protein** leads to **immunogenic reaction.** • If binding to DNA become carcinogenesis.	**Weaker** than the covalent • Lipid peroxidation generation of cytotoxic oxygen radicals. • Impairment of mitochondrial respiration. • Depletion of GSH reactions leads to oxidative stress. • Modification of sulfhydryl groups impair Ca2+homeostasis. • Protein synthesis inhibition.

Do hepatotoxins cause liver disease in all people?

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

Environmental host factors	Host genetic makeup
• Race • Age • Sex • Nutritional status • Drugs • Concomitant habits • Diseases	• Metabolizing Enzymes • Detoxifying System • Drug Transport

Drug-induced hepatic injury (DIHI)

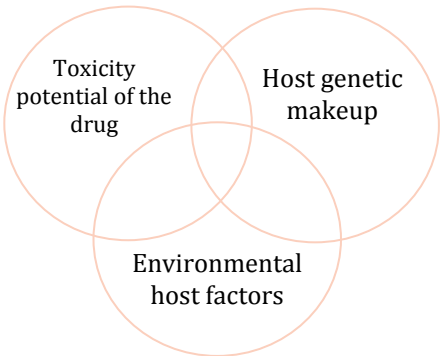
Is DIHI common ?

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

Are certain persons or population more susceptible ?

Upon exposure to hepatotoxins people are categorized as:

1. Tolerators: No injury.
2. Adaptors: Mild transient injury but adapt.
3. Susceptibles: **Develop overt symptoms depending on existing** predisposing factors.
4. In Threat: **DILI** accelerates beyond initial targets due to loss of synthetic & clearance function of hepatocyte. with recruitment of inflammatory cells provoke. apoptotic & necrotic signals.



What are the presenting manifestations ?

Individual drugs tend to haven CHARACTERISTIC SIGNATURE:

A particular latency period | **A clinical pattern** | **A particular pathological finding**

Latency period

- **Short (hrs/days)**
- **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 withdrawal → amiodarone(cumulative)/phenytoin, isoniazid (idiosyncratic)

In indirect metabolic idiosyncratic hepatotoxicity → latency period → usually long → unpredictable → most problematic → tetracycline, oral contraceptives.

Clinical pattern

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

Some drugs just induce: Asymptomatic increase in the enzymes (Aminotransferase)

1. Phenytoin.
2. Statins.
3. Sulfonamides.
4. Sulfonylureas.

Other drugs induce symptomatic manifestations

- If injury targets **hepatocytes** → apoptosis or necrosis → HEPATITIS (cytotoxic) develops → rapid onset of malaise, severe **anorexia** and **jaundice** + increase in **alanine aminotransferases (ALT)**
- If injury targets biliary system (canalicular or ductal) → CHOLESTASIS develop → **jaundice** + severe **pruritus** predominate → ↑ **in alkaline phosphatase (ALP) + hyperbilirubinemia.**
- if injury targets both hepatocytes & biliary system → **MIXED TYPE.**

Some Patterns of symptomatic drug-induced liver disease

So important

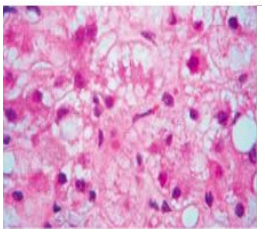
Hepatic injury	Hepatocellular	Cholestatic	Mixed
symptomes	**Flu-like**, **malaise**, m. aches weakness, **loss of appetite**, GIT symptoms, diarrhea, **jaundice**, urine discolored.	**Yellowish discoloration of skin**, dark urine, rash, **pruritus**, stool may be light	The pt will present with mixed symptoms and **both (ALT.ALP) will be elevated**
ALT	≥ 3 fold rise	Normal or slight	≥ 3 fold rise
ALP	Normal	≥ 2 fold rise	≥ 2 fold rise
Examples	1. Acetaminophen 2. NSAIDs 3. Isoniazid 4. Amiodarone	1. Chlorpropamide 2. Erythromycin 3. Rifamycin 4. Oral contraceptives	1. Phenytoin 2. Carbamazepine 3. Sulfonamides 4. ACE Inhibitors

Histopathological Patterns

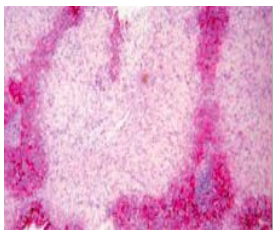
Not important

No universal histopathological pattern of DIHI exist
The **commonest** are;
1-Hepatocellular necrosis
2- Cholestasis
3-Steatosis (fat)

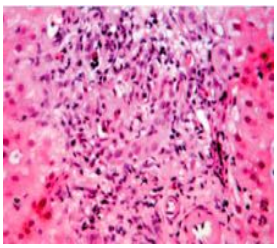
-More than one type of injury may occur in the same patient
-Any one agent may produce different types of injury in different patients



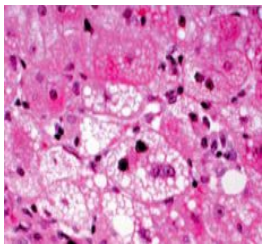
Ballooning & degeneration of hepatocyte



Centrilobular & Midzonal necrosis



Cholestatic injury with damaged bile duct



Fatty accumulation

Lines of treatment

Immediate withdrawal ⟶ **Of any suspected drug**

No Specific treatment ⟶ **Largely 1-Symptomatic & 2-Supportive**

1-Symptomatic:

1. Severe allergic reaction is observed (Corticosteroids)
2. Pruritus - enhance bile acid secretion (Cholestyramine) **important**
3. Cholestatic liver injury (ursodeoxycholic acid (Ursodiol) **important**
4. Coagulopathy or encephalopathy develop (treat accordingly)

2-Supportive:

- High carbohydrate
- Moderate protein diet
  Adequate in calories

Specific Antidotes:

1-N-acetylcysteine for acetaminophen toxicity
2-L-carnitine for valproate toxicity
} **So Important**

Emergency liver transplantation For drug induced fulminant hepatic failure

Cases from Dr slides

Case 1

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 flu 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 arthritis 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. Multivitamins
C. Isoniazid D. Domperidone

Answer is (C)(isoniazid)

Which type of hepatotoxin is it considered?

Immunoallergic Idiosyncratic

What is the likely hepatotoxic pattern inflicted by the drug?

Hepatocellular / Viral Hepatitis-like pattern

Case 2

A hypercholesterolemic patient was received in E.R complaining of yellowish discoloration of skin, change in color of urine & stools, and severe itching

He has been receiving **statins** for the long time for the hypercholesterolemia. 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 **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 drugs is the likely cause of his symptoms?

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

Answer is (B)(Chlorpropamide)

Which type of hepatotoxin is it considered?

Immunoallergic Idiosyncratic

What is the likely hepatotoxic pattern inflicted by the drug?

Inflammatory Cholestasis

Summary

<table>
<tr><th colspan="3">Summary of Types Of Hepatotoxins</th></tr>
<tr><th></th><th>Intrinsic Hepatotoxin</th><th>Idiosyncratic Hepatotoxin</th></tr>
<tr><td>Cause</td><td>Direct Hepatotoxicity</td><td>Indirect Hepatotoxicity</td></tr>
<tr><td>Type</td><td>TYPE A Adrs:
• Predictable / Direct
• Dose-dependent Hepatotoxicity</td><td>TYPE B Adrs:
• Unpredictable / Bizarre / Idiosyncratic
• Dose-independent Hepatotoxicity</td></tr>
<tr><td>Dose</td><td>Supratherapeutic Or Cumulative Dose Of The Drug</td><td>Normal Dose Of The Drug</td></tr>
<tr><td rowspan="6">Drugs</td><td>Direct increased dose dependent hepatotoxicity</td><td>Hypersensitivity or immunoallergic reaction</td></tr>
<tr><td>• Acetaminophen
• Salicylates
• Statins(Hyperlipidemia)</td><td>A drug or its metabolite binds to hepatic membranes or proteins act as hapten to induce a variety of immune reactions
<table><tr><th>Inflammatory cholestasis</th><th>Viral hepatitis-like pattern</th></tr><tr><td>-Chlorpromazine.
-Chlorpropamide.
-Erythromycin.</td><td>-Isoniazid.
-Phenytoin.
-Methyldopa.</td></tr></table></td></tr>
<tr><td>Direct cumulative hepatotoxicity</td><td>Metabolic Idiosyncratic Hepatotoxicity</td></tr>
<tr><td>• Amiodarone
• Oral contraceptives</td><td rowspan="3">The metabolite of the offending drug interferes with hepatic metabolism as that of bilirubin or protein synthesis….etc
<table><tr><th>Interfere with bilirubin metabolism</th><th>Interfere with protein synthesis</th></tr><tr><td>-Erythromycin.
-Rifampicin.</td><td>-Corticosteroids.
-Tetracycline.</td></tr></table></td></tr>
<tr><td>Mixed</td></tr>
<tr><td>• Methotrexate
• Alcohol</td></tr>
</table>

Summary

Some Patterns of symptomatic drug-induced liver disease			
Hepatic injury	**Hepatocellular**	**Cholestatic**	**Mixed**
symptomes	**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
Examples	1. Acetaminophen 2. NSAIDs 3. Isoniazid 4. Amiodarone	1. Chlorpropamide 2. Erythromycin 3. Rifamycin 4. Oral contraceptives	1. Phenytoin 2. Carbamazepine 3. Sulfonamides 4. ACE Inhibitors

Summary

Summary of "What are the presenting manifestations?"			
Drug	**Individual drugs tend to have → CHARACTERISTIC SIGNATURE**		
Duration	short(hrs/dys)	intermediate (1 -8ws)	long (1-12ms)
Latency period	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 presents	Some drugs just induce → ASYMPTOMATIC Manifestations → increase in aminotransferases (Ex. Phenytoin, Statins, Sulfonamides, Sulfonylureas).		
	Other drugs induce → SYMPTOMATIC MANIFESTATIONS 1- If injury targets hepatocytes → apoptosis or necrosis → HEPATITIS (cytotoxic) develops → rapid onset of malaise, severe anorexia and jaundice + increase in alanine aminotransferases (ALT). 2-If injury targets biliary system (canalicular or ductal) → CHOLESTASIS develop → jaundice (+or-) severe pruritus predominate → increase in alkaline phosphatase (ALP) (+or-) hyperbilirubinemia. 3- If injury targets both hepatocytes & biliary system → MIXED TYPE.		
Lines of treatment	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 Supportive; High carbohydrate, moderate protein diet adequate in calories.		
	Specific antidotes N-acetylcysteine → acetaminophen toxicity. L-carnitine → valproate toxicity.		
	Emergency liver transplantation → for drug induced fulminant hepatic failure		

MCQs

Q1-Which one of the following is a specific antidote for acetaminophen toxicity?

A- L-carnitine B-N-acetylcysteine

C-Ursodeoxycholic acid (Ursodiol) D-Corticosteroids

Q2-Patient came with symptoms of cholestatic liver injury, which of the following should be given to him?

A- L-carnitine B-Cholestyramine

C-Ursodeoxycholic acid (Ursodiol) D-Corticosteroids

Q3- A 63-year-old man presents to the emergency department with altered mental status after ingesting an entire bottle of acetaminophen. The patient's heart rate is 120 beats/minute, blood pressure is 100/58 mm Hg, and respiration rate is 28/minute. His aspartate aminotransferase and alanine aminotransferase are 4,128 IU and 3,978 IU, respectively. What is the most appropriate treatment for this patient?

A- Ammonium chloride B- L-Carnitine

C- N-Acetylcysteine D- Noaloxone

Q4- A56-year-old man who is an alcoholic presents to the emergency department with altered mental status. Blood tests reveal normal creatinine but hyperammonemia. He is admitted to the hospital for treatment. He has several comorbidities that are being managed well as an outpatient. His wife brings a list of his home medications, which includes bimatoprost, simvastatin, alprostadil, aspirin, and lisinopril. Which of the following should be held (not given to him) during his hospital stay?

A- Alprostadil B- Simvastatin

C- Bimatoprost D- Lisinopril

Q5- 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

Q6- According to Q5, which type of hepatotoxin is considered?

A- intrinsic cumulative B- Immunoallergic Idiosyncratic

C- metabolic idiosyncratic D- Intrinsic Supratherapeutic

Q7- A patient took an increased dose of drug A, after one hour he developed anorexia and muscle aches, what is drug A?

A- Acetaminophen B- Rifampicin

C- Phenytoin D- Corticosteroids

Q8-According to Q3, what is the treatment?

A- N-acetylcysteine B- Cholestyramine

C- L-carnitine D- Corticosteroids

8-A
7-A
6-B
5- B+D
4-B
3-C
2-C
1-B

SAQ:

20 years old patient has joint pain one day he experienced severe pain and he took overdose from The prescribed drug ,then he developed Diarrhea ,janduce and malaise.

What's the causative drug?

Acetaminophen

What type of toxicity does it cause to the liver?

Direct increased dose dependent hepatotoxicity

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References:

✓ Doctors' slides and notes

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