

Hepatotoxicity

Presented

By

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Learning objectives

- ✗ Definition
- ✗ •Mechanism of hepatotoxicity
- ✗ •Metabolism of drug
- ✗ Mechanism of drug induced hepatotoxicity
- ✗ Risk Factors of hepatotoxicity
- ✗ Manifestations of hepatotoxicity
- ✗ Common agents causing hepatotoxicity
- ✗ Management of drug induced hepatotoxicity



Definition

- ✘ **Capacity of the drug, chemical, or other agent exposure to induce liver damage (injury).**



**Disruption
of
hepatocyte**

**T-cell
activation**

**Disruption
of
Transport
proteins**

Mechanism of Hepatotoxicity

**Apoptosis
of
hepatocyte**

**Mitochondrial
disruption**

Bile duct injury

Metabolism of drug

Phase 1

Drug



Catalyze by P-450 enzymes



Oxidation or Hydroxylation



Intermediate reactive product



End metabolite(Toxic)

Phase 2



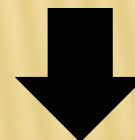
Conjugation



**With
glutathione
glucuronic acid**



**Increase of
solubility of drug**



**Excretion in bile
or urine**

Mechanism of drug induced hepatotoxicity

Overlapping mechanism (halothane)

Idiosyncratic drug reactions

- Hypersensitivity** (Phenytoin)
short period of 1-4 weeks
- Metabolic-idiosyncratic** (INH)
one week up to one year

Intrinsic drug reactions

- Dose dependant
- due to drug or metabolite
- Acetaminophen-carbon tetrachloride

Risk Factors

1. **Age**
2. **Sex**
3. **Race**
4. **Alcohol**
5. **Liver disease**
6. **Genetic factors**
7. **Malnutrition (paracetamol)**
8. **Other diseases (AIDS), diabetes, renal failure**
9. **Long acting drugs**



Clinical manifestations

Pathological manifestations



**Manifestations of drug induced
hepatotoxicity**

Pathological manifestations

Acute hepatocellular injury

Spotty necrosis - Liver failure

INH

Chronic hepatocellular injury

Pigment accumulation

Fibrosis and cirrhosis -Steatosis

Alcohol

Acute and chronic cholestasis

Amoxicillin - clavulanic acid

Chlorpromazine

Hepatitis

Granulomatous

carbamazepine

Autoimmune

Sulfonamide

Vascular injury

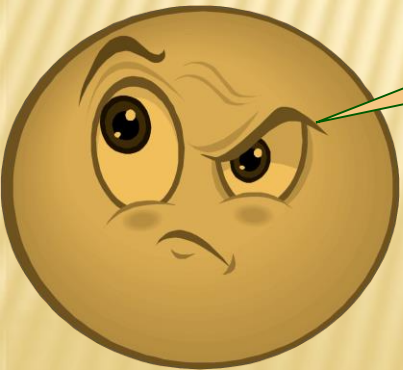
Steroids

Neoplastic lesions

Oral Contraceptives

Clinical manifestations

1. Asymptomatic elevation of liver enzymes
2. Elevations of AST, ALT
3. Elevation of bilirubin level
4. Elevation of ALK.Ph
5. Extra-hepatic manifestations



Common Hepatotoxic agents

Paracetamol – Diclofenac
Aspirin

Ciprofloxacin-INH

Amoxicillin – Erythromycin

Rifampin

Methyldopa- Statins

Chlorpromazine

Oral contraceptives

Fluconazole

Carbon tetrachloride

Alcohol-Aflatoxins

DIAGNOSIS

History taking



Examination



liver function testes



Radiological investigations



Ultrasound -CT- MRI



Liver biopsy

Management

Diagnosis
History
Examination
Investigation

Treatment

Prevention

TREATMENT

- ✘ **Stop the drug**
- ✘ **Supportive (symptomatic)**
- ✘ **Specific therapy**
 1. N- acetylcysteine (Paracetamol)
 2. L-Carnitine (Valporic acid)
 3. Corticosteroids (allergic reaction)
 4. Liver transplantation (fulminant hepatic injury)

PREVENTION

- ✘ Adjust dose
- ✘ Assess hepatic function
- ✘ Avoid hepatotoxic combinations
- ✘ Correct risk factors
- ✘ Use non-hepatotoxic drugs

Thank you

Thank you



Thank you

Thank you