Drugs and liver

By

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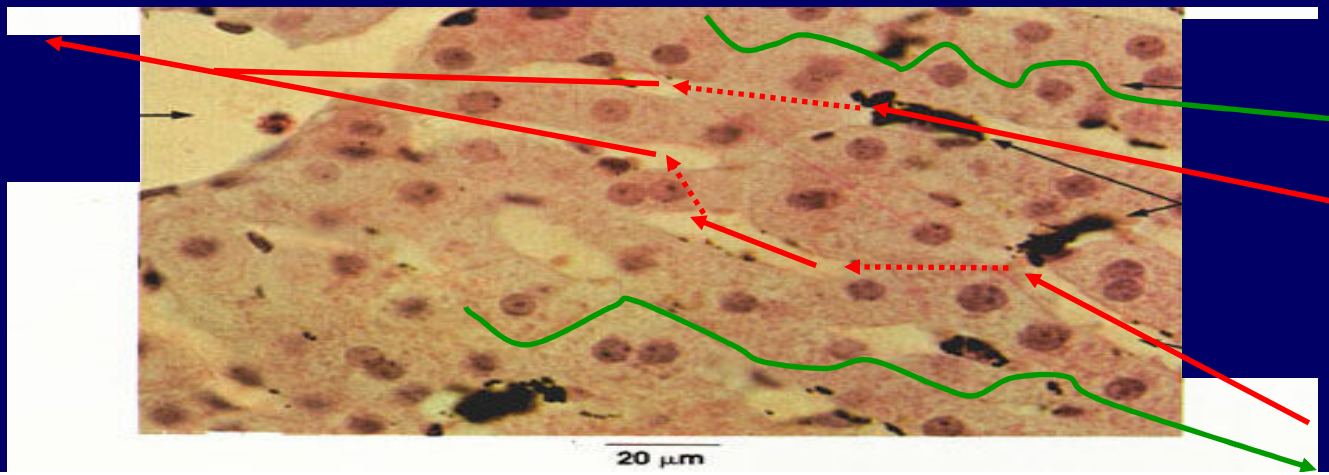
Objectives of the lecture (drugs and liver)

1. Explain why the liver is the most commonly affected organ by drugs
2. Explain how the normal liver can handle different drugs
3. Enumerate the factors affecting drug metabolism in the liver
4. Enumerate the risk factors increasing drug-induced liver injury
5. List the most common hepatotoxic drugs
6. Explain the mechanisms of drug-induced hepatotoxicity.
7. Enumerate types of drug-induced liver disease (DILD)
8. Describe the characters of DILD
9. Explain how to identify and monitor drug-induced hepatotoxicity
10. Outline a general plan for treatment of DILD and how to minimize its risks.
11. Explain the pharmacokinetic and pharmacodynamic changes of drugs in cases of liver disease.
12. Give guidelines for prescribing drugs for treating the most common diseases of body systems (infections, CVS, CNS, GIT, Endocrine, Respiratory) in case of liver disease like cirrhosis and hepatic failure.

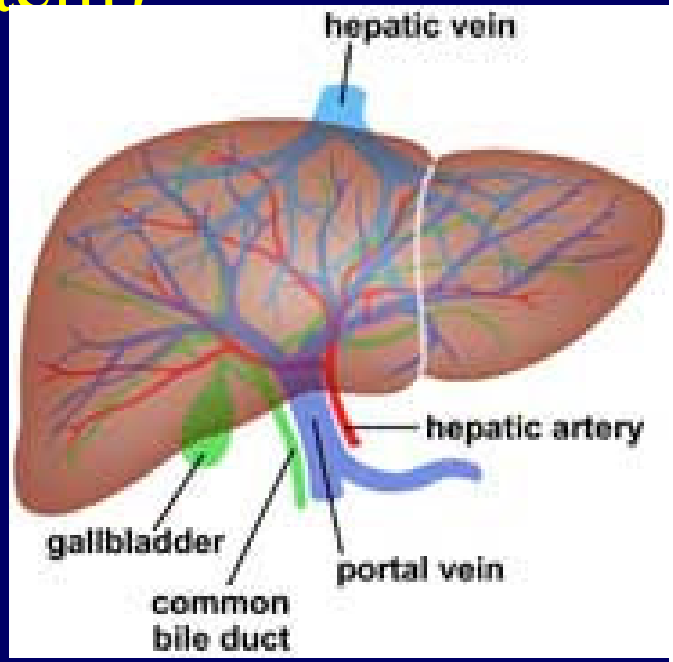
Some facts about drugs and liver

1. Drugs ► Hepatic injury 6% of all & 15% of lethal **adverse drug reactions**
2. Drugs cause **5% jaundice**, **10% hepatitis**, **40% ALCF** with fatality in **50%**
3. **600 drugs** involved (paracetamol, Anti TB, Cytotoxic, antibiotics, psychotropic)
4. Paracetamol overdose► ½ cases of ALCF



Why liver is more Vulnerable to drug injury

1. **High exposure**: Oral 100%- parenteral 25% CO
2. **Rapid extensive uptake and metabolism** of drugs (anatomy)(sinusoids & fenestrations-brush border►↑SA-▲Intracellular enzyme activity-Connected to bile system)
3. How drug uptake occurs in liver?
4. What are the phases of metabolism?
5. Which phase is affected first in LD?
6. What are the products of metabolism?
7. What are the factors affecting drug metabolism?



The relation between liver and drugs

A. Drugs ►liver disease
B. Liver disease ►affect **pharmacokinetics** and **pharmacodynamics** of drugs changes in drug effects

Drug-induced liver disease

Risk factors of drug-induced liver disease:

1. **Pre-existing liver disease**
2. **Age**: eldely (except < 3 years (valproate, aspirin (Reye's syndrome)
3. **Gender:** Females> males (halothane, INH), Co-amoxiclav (Males)
4. **Genetics**: slow & rapid acetylators (INH)
5. **Enzyme induction**: Alcohol & Rifampicin # Paracetamol & INH
6. **Polypharmacy**: Anti-TB, NSAIDS
7. **Concurrent disease & pregnancy**: Kidney, DM, organ transp.
8. **Drug dose and duration**
9. **Poor nutritional status**: Fasting, ▼ Vit.c, Vit.E, ▲High iron, transferrin, selenium

Mechanisms of drug-induced liver disease

1. **Products of phase I** are reactive **electrophiles**, free radicals►bind to cell membranes, disrupt their function►hepatocellular necrosis. E.g. Paracetamol, **INH (CM, mitochondria, degradation enzymes, immunoallergic mechanisms)**

2. **Inadequate detoxification** by phase II reactions like reduced binding substances (glutathione) e.g. phenytoin

Types of drug-induced liver disease

	Liver disease	Drugs associated
1	Hepato-cellular necrosis	Paracetamol, INH, salicylates,.
2	Fatty liver	Amiodarone, tetracycline, steroids , Alcohol
3	Cholestasis	Oral contraceptives, anabolic steroids, cyclosporin
4	Cholestasis with hepatitis	Chlorpromazine, TCA, Niacin erythromycin, flucloxacillin,
5	Granulomatous hepatitis	Phenytoin, allopurinol
6	Acute hepatitis	Isoniazid, phenytoin, dantrolene
7	Chronic active hepatitis	Methyldopa, nitrofurantoin, INH
8	Fibrosis and cirrhosis	Methotrexate, Methyldopa, Vit A (dose-related), Alcohol.
9	Vascular disorders (veno-occlusive diseases)	Azathioprine, dactinomycin,, OCP
	Tumors	OCP, anabolic steroids,

Classification of drug-induced hepatic damage

	Type A (predicted)	Type B (idiosyncratic)
incidence	More common (All individuals)	Less common (1% those taking drugs)
Predictability	Predicted	Unpredicted
Dose-related	Dose-dependent	Not dose-dependent (therapeutic)
Mechanism	1. Cytotoxic: paracetamol 2. Cholestatic: Sex hormones	1. Hypersensitivity (valproate) 2. metabolic abnormality (Ketoconazole)
Latency period	Short latency period (hours)	Variable latency period (Weeks or Months)
Type of injury	Usually necrosis	Any
Associated	Acute liver failure	May be; Allergy-esinophilia-lymphadenopathy
Examples	Paracetamol, tetracyclines, methotrexate, Salicylates	Halothane, INH, methydopa

Hepatic toxic doses of some drugs

	Drug	Toxic dose
1	Paracetamol	> 10 gm
2	Tetracyclines	> 2gm daily, ↑Renal & pregnancy
3	Methotrexate	Weekly dose > 15 mg or 2gm in 3 years
4	Vit. A	Chronic use of 40.000 U daily
5	Salicylates	Chronic use > 2gm daily
6	Iron	Single dose > 1gm
7	Cyclophosphamide	Daily dose of > 400 mg/m^2
8	Anabolic steroids	High dose > 1 month
9	Oral contraceptives	Old preparations, high estrogen

Some points related to drug-induced injury

1. **Mention 7 effects of alcohol on liver?** Hypoglycemia, lactic acidosis, fatty liver, hepatitis, induction of CYP, inhibition of CYP, Cirrhosis
2. The more cytotoxic the injury the **more likely** is the hepatic failure and death
3. The more c**holestatic** the injury **the better** the prognosis
4. **When to think in dug-induced liver disease?**
    1. Raised liver enzymes (transaminases)
    2. Unexplained jaundice
    3. Acute hepatitis, chronic active hepatitis, cirrhosis
    4. Primary hepatic tumors
    5. Liver disease of unknown origin

How to identify hepato-toxicity?

1. **Drug history**: Very important (all drugs, OTC, OCP, herbs), Onset of symptoms, allergic manifestations, predisposing factors, improvement on withdrawal.
2. **History of toxin exposure**: Arsenic, copper
3. **Exclusion of other causes**: viral hepatitis (serological markers), stones
4. **Monitoring of the liver function tests** during hepatotoxic drugs taking like INH

    a. **Predictable**: LFTs for hepatotoxic drugs

    b. **Idiosyncratic** : not valuable

5. **Radiological investigations** (CT, US, ERCP)
6. **Liver biopsy**: e.g. methotrexate, tetracyclines (steatosis)
7. **Diagnostic challenge**: dangerous

Treatment of drug-induced liver disease

1. **Correct diagnosis** (History)
2. **Withdrawal** of the causative drug
3. **Supportive therapy:**
    1. **Removal** of the drug from the body (paracetamol acute)
    2. **Antidote**: e.g. acetylcysteine for paracetamol, desferrioxamine
    3. **Corticosteroids**: Hypersensitivity
    4. **Good diet**: High in CHO, Low fat
    5. **Fluid & electrolytes**
    6. **Treatment of pruritis**: How?
    7. **Treat coagulation disorders**: e.g. Vit. K, FFP
    8. **Long-term treatment:** Avoid similar drugs (class) e.g. halothane, NSAIDs, Tricyclics, phenothiazines
4. **Liver transplantation**: in cases of AHF

How to minimize the risk of drug-induced hepatotoxicity

1. **Restrict use of hepatotoxic drugs:**

   like co-amoxiclav < 14 days

2. **In operations, avoid repeated using of halothane in anesthesia:**

   especially if there were symptoms or family **history. Use isoflurane but better IV anesthesia like propofol**

3. **All new drugs:**

   should be tested for hepatotoxicity: e.g. **troglitazone** and followed.

4. **Appropriate selection of drugs:**

   awareness of the predisposing factors, avoidance of toxic doses, and hepatotoxic drug-drug interactions

5. **Regular monitoring of liver function tests:**

   in patients taking hepatotoxic drugs like anti-TB, and anti-epileptic drugs, methotrexate, sulfasalazine, amiodarone, methyldopa, valproate

Effect of liver disease on drugs

A. Pharmacokinetics:

Occurs in cases of severe liver disease (**Cirrhosis. (Coagulation dist., jaundice, CAH) less with AH, biliary obstruction)**

Changes which occur in SLD:

a. Loss of **fenestrations** of endothelium
b. **Delayed diffusion** across space of Disse. **Why?**
c. Loss of **brush border** of hepatocytes
d. Reduced intracellular **metabolizing enzymes**
e. Decreased **hepatic blood flow**
f. **Porto-systemic shunts:** By pass 60%

1. **Absorption:** Not greatly affected
2. **Distribution: ▼**PP, **▲**bilirubin. What is the effect?
3. **▼Metabolism: ▼**70% of metabolism, Bioavailability **▲**5-folds
4. **▼Biliary excretion:** e.g. Rifampicin, fucidic acid
5. **▼Production of bile**: What is the effect? **▼ADEK**
6. **▼Kidney function: Hepatorenal syndrome**

Patterns of pharmacokinetic changes in liver disease

A. **Rapidly metabolzing drugs (1st pass metabolism drugs) → Dependent on hepatic blood flow:** increased oral systemic bioavailability → increased effect e.g. labetalol, propranolol, pethidine, amitryptyline, isoniazid, verapamil, morphine, imipramine (***What we do?)***

B. Slowly metabolizing drugs (depend on the metabolic capacity) show prolongation of half life :

like diazepam, lorazepam, phenobarbitone, theophylline, clindamycin.***(What we do?)***

B. Pharmacodynamic changes occur in CLD

1. **Cellular response to drugs may alter,** e.g. CNS depressants sensitivity to opioids, sedatives, antiepileptic is **increased→ hepatic coma (2 reasons)**
2. **Effect of oral anticoagulants is increased**? **Why? 2 reasons.** (aspirin, NSAIDs, warfarin)
3. **Fluid and electrolyte balance is altered,** e.g. fluid retention by NSAIDs and cortisone. **Why?**
4. **Ascites & edema** become more resistant to diuretics. ***Why?.***
5. **Diuretics** ppt coma in liver cirrhosis**. Why?**
6. **Drugs which induce constipation ppt coma. Why?**

Prescribing of drugs in patients with liver disease

1. ***Are there calculation of drugs in cases of liver disease like that in cases of CRF? Why?***
2. If liver disease is **stable** and well **compensated**, prescribing of most drugs is **safe**.
3. **Conditions which need care are:**
    1. Impaired hepatic **synthetic** function (albumin, coagulation factors)
    2. Hepatic **encephalopathy** (**current or recent**)
    3. **Fluid retention** or renal impairment
    4. **Drugs with**:
        1. high hepatic extraction (Reduce the dose to 25-50% of normal
        2. High plasma protein binding (phenytoin)
        3. Low therapeutic ratio (theophylline)
        4. CNS depressant effect (Hypnotics)

Prescribing drugs in cases of liver disease

	System	Drugs avoided	Drugs could be prescribed
1	CNS	Sedatives, Antidepressants, antiepileptics, analgesics	Midazolam, paroxitine, phenytoin, paracetamol, colchicine
2	CVS	K. wasting diuretics, Anticoagulants, B.blockers, CCBs	Spironolactone, ▼Dose, ▼dose
3	GIT	Na-containing antacid Al-containing antacids Antimotility Antiemetics	Lactulose Domperidone
4	Infections	Hepatotoxic (INH, erythromycin, rifampicin, tetracyclines, Ketoconazole, Na penicillins))	Penicillins, some cephalosporines gentamycin
5	Endocrine system	Anabolic steroids, OCP, androgens, metformin, sulphonylurea	Repaglinides, glipizide, Insulin
6	Respiratory	Theophylline	▼Dose