6) Drugs, Toxins & the Liver – Dr. Muhamamd Omar

The liver is the main organ in which drugs are metabolized & consequently is important in determining the effects of drugs in the body. Hepatic drug metabolism involves the conversion of fat- soluble (non- polar) drugs in to H2O- soluble (polar) metabolite which can be excreted in the bile if they are relatively large molecule or in the urine if they are relatively small.

Two-type reaction takes place during hepatic drug metabolism:

- **Type 1:** mainly involve oxidation or reduction to increase drug polarity & provide drug for subsequent type 2 rxns.
- **Type 2:** involve conjugation, which lead to production of highly polar metabolite, which are excreted in bile or urine.

The rate of drug metabolism vary depending on: 1. Genetic factor 2. Nutritional factor 3. Induction or inhibit of the enzyme 4. Numbers of drugs given simultaneously 5. Hepatic blood flow.

Drugs which are hepatic enzyme inducer: Alcohol, Barbaturate, Carbamazepin, Phenytion, Rifampicin, Primidone.

Drugs which are hepatic enzyme inhibitor: Cimetidine, INH, Ketoconazole.

Clinical points: Jaundice, Ascites, Encephalopathy, Fetor hepaticus, palpable spleen, Malnutrition.

Investigation: Hypoalbuminemia, prolong P.T, Esophageal varices.

Hepatotoxic drug reactions

Possibility of Drug toxicity should be high in the differential diagnosis of acute liver failure, jaundice and abnormal liver biochemistry. The most common picture is a mixed cholestatic hepatitis. The presence of jaundice indicates more severe liver damage. Although acute liver failure can occur, most drug reactions are acute and self-limiting; chronic liver damage is rare. LFTs often take weeks to return to normal following a drug-induced hepatitis and it may take months for them to normalize following a cholestatic hepatitis. Occasionally permanent bile duct loss (ductopenia) follows a cholestatic drug reaction, such as that due to co-amoxiclav, resulting in chronic cholestasis with persistent symptoms such as itching.

Hepatotoxicity Pattern	Drug
Cholestasis	Chlorpromazin, Estrogens
Cholestatic hepatitis	NSAIDs, Co-amoxiclav, Statins
Acute hepatitis	Rifampicin,Isoniazid
Non-alcoholic steatohepatitis	Amiodarone
Venous outflow obstruction	Busulfan, Azathioprine
Fibrosis	Methotrexate

Acute hepatic damage

Is the best-recognized form of drug induced liver injury, such damage may be:

1. Dose- related & predictable; hepatotoxicity is mediated biochemically. E.g./paracetamol poisons.
2. Unrelated to dose & unpredictable or idiosyncratic; (infrequent, occur at any time, associated with fever, rash, arthralgia & eosinophilia). Unpredictable or idiosyncratic drug hepatotoxicity attributed to immunological injury or may be associated with Antibody- formation. / Halothane hepatitis. Jaundice is usually present & is usually indistinguishable from viral hepatitis.

Drugs to avoid in cirrhosis

- Most analgesics can precipitate complications and need to be used cautiously in cirrhosis. NSAIDs are hepatotoxic and can potentiate Hepatorenal failure; they should therefore be avoided in cirrhosis.
- Paracetamol up to a dose of 3 g/day can be used safely in chronic liver disease but higher doses may result in acute hepatic necrosis, particularly in patients with alcoholic liver disease.

Drug	Problem	Toxicity
NSAIDs	Reduced renal blood flow	Hepatorenal failure, bleeding varices
ACEI	Reduced renal blood flow	Hepatorenal failure
Codeine, Narcotics	Constipation	Hepatic encephalopathy
Anxiolytics	Accumulation	Hepatic encephalopathy