2011a(3): Outline the effects of liver failure on drug kinetics and dynamics

General
Liver failure: impaired metabolic and synthetic functions of the liver. Effects are direct & indirect

Pharmacokinetics
Absorption
- May be decreased 2° to ↓bile for fat soluble vitamins
- High first pass metabolism drugs may have ↑oral bioavailability as metabolism ↓
  - Eg. Morphine, midazolam, labetolol
- High clearance (HER) drugs may have ↑systemic availability 2° to portocaval shunting

Distribution
- Volume of distribution ↑
  - ↑total body water: ascites/oedema
  - ↓protein binding (protein synthesis in liver)
    - albumin t₁/₂ = 23d
      - ↑unbound acidic drugs
    - α acid glycoprotein
      - ↑unbound basic drugs
      - ↑toxic effects eg. Phenytoin

Metabolism
- Low HER drugs
  - Decreased enzymatic degradation
  - Prolonged action of drug
  - Oxidation reactions impaired more than conjugation
- High HER drugs
  - Decreased clearance due to decreased blood flow
  - ↓pseudocholinesterase levels
    - t₁/₂ 14d
    - prolonged NM block with sux and mivacurium
    - prolonged action of remifentanil

Excretion
- ↑renal excretion of drugs not bound by plasma proteins
- ↓biliary excretion (obstruction)
- renal failure (hepatorenal syndrome) → decreased excretion

Pharmacodynamics
CNS
- hepatic encephalopathy
- Pre-encephalopathy - ↑sensitivity to centrally acting drugs eg. Opiates and benzodiazepines

Haematology
- ↑sensitivity to oral anticoagulants-clotting factor synthesis already reduced

Metabolic state
- diuretics precipitate encephalopathy due to hypokalemic alkalosis

Fluid overload
- exacerbated by drugs that cause fluid retention eg. NSAIDs, antacids

Hepatotoxic drugs
- should be avoided
- sulfonamides, rifampicin, halothane
- ↑risk of hepatotoxicity

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