1995b(13): Give a brief account of drug protein binding and outline its significance

General: Drug protein binding refers to the interaction a drug has with proteins.
- Can be intravascular, interstitial, or intracellular proteins
  - Plasma proteins binding is most significant
- Interaction is usually reversible
- Ionic or electrostatic
- Obeys the law of mass action
  \[ \text{[drug]} + \text{[protein]} \leftrightarrow \text{[drug.protein]} \]

**Plasma Protein Binding**

**Albumin**
- Present in high conc (40g/L)
- Binds neutral/acidic drugs (eg barbiturates)
- 2 important binding sites → (I) warfarin and (II) BZ
- Drugs compete for these sites
  - Binding readily reversible, therefore can affect active unbound fraction of drug
- Binding at other sites on the molecule can change conformation of molecule and affect binding at the warfarin and BZ binding sites

α₁-acid glycoprotein
- Low conc, low capacity
- Most important of the plasma globulins
- Binds basic drugs (LAs, morphine)
- **Acute phase reactant**

**Lipoproteins**
- Not true binding
- Function to partition highly lipophilic drugs (eg fentanyl)

**Extent of protein binding determined by:**

**Drug characteristics**
- Affinity for protein
- Conc of drug
- pKa relative to pH of plasma: ↑ionised → ↑protein binding, ↑unionised → ↑partitioning of drug
- Presence of other drugs competing for same site

**Protein characteristics**
- Conc
- Number of available binding sites → Altered by conformational changes

**Significance**
- Vd: ↑protein binding → ↓Vd as remains in vascular compartment
- Clearance: ↑protein binding → ↓renal/hepatic clearance
  - BUT propofol 98% protein bound AND rapidly metabolised HER1.0
    - 2° rapid equilibrium of bound/unbound drug
- Drug action: only unbound fraction of drug pharmacologically active

**Altered states of protein binding**
- Pathological states: end-stage liver failure, burns → ↓protein binding
- Inflammation: ↑protein binding as proteins are acute phase reactants

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