2008b(2): Describe the pharmacokinetic principles of total intravenous anaesthesia using propofol.

**General:** Total intravenous anaesthesia (TIVA) is the method of inducing and maintaining general anaesthesia via a continuous infusion of an IV anaesthetic agent (namely propofol) without the use of an inhaled volatile anaesthetic agent.

**Aim:** The goal of TIVA is to reach and maintain a central compartment or effect site concentration of propofol at a level adequate for anaesthesia.

**Propofol:**
- **Structure:** propofol is a sterically hindered phenol (2,6-diisopropylphenol)
- **Uses:**
  - induction and maintenance of general anaesthesia
  - IV sedation in the operating theatre and ICU
  - refractory nausea and vomiting
  - status epilepticus
- **MOA:** potentiate GABA effect on GABA<sub>α</sub>R
- **Doses:**
  - induction 1-4mg/kg (↑dose required in children and some adults)
  - maintenance 4-12mg/kg/hr
- **Pharmacokinetics:**
  - **Absorption:**
    - IV only
  - **Distribution:**
    - Vd huge >700L
    - 98% protein bound (albumin)
    - highly lipophilic
    - t<sub>1/2α</sub> ~1.5min
  - **Metabolism:**
    - hepatic (CYP450) + ?extra-hepatic clearance (Cl>Q-liver)
    - clearance ~ 30ml/kg/min
    - inactive metabolites
  - **Elimination:**
    - urine (inactive metabolites, 0.3% unchanged)
    - ↓rate of elimination in renal disease (does not effect action)

**First Stage:**
- when given as an infusion propofol will initially be given as a loading dose to fill the central compartment and bring about its clinical effect via its concentration at the effect site
- a large loading dose is required due to the high lipid solubility and central compartment Vd of propofol

**Second Stage:**
- propofol will then distribute to the peripheral compartments reducing plasma concentration and also begins to undergo metabolism further reducing the plasma concentration

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the rate of the propofol infusion is then adjusted to take into account the effects of distribution and metabolism in order to maintain a steady plasma or effect site concentration

Third Stage:
- if propofol is continued to be infused it will continue to distribute and saturate the peripheral compartments
- therefore an infusion of propofol results in clearance becoming the 1° determinant of plasma or effect site concentration as the peripheral compartments become saturated
- this is different from when propofol is given as a bolus as its offset of action is 1° due to distribution (t_{1/2α} ~1.5min)

Propofol Infusion:
- results in an ↑ context-sensitive half-time (CSHT)
- CSHT is the time taken for the plasma concentration of a drug to fall to half of the value at the time of stopping an infusion
- the ‘context’ refers to the duration of the infusion
- relates distribution and re-distribution to and from peripheral compartments and the clearance of a drug in a multi-compartmental model
- once an infusion of propofol is stopped re-distribution of the drug from the peripheral → central compartment will maintain plasma or effect site concentration and clinical effect
- in general, short infusions that have not reached steady-state will have a CSHT approaching t_{1/2α} (duration of action dependent on time taken for redistribution), whereas infusions that reach steady-state will have a CSHT that approaches t_{1/2β} (elimination half-life: time taken to achieve 50% plasma concentration by removal of drug from the body during the elimination phase)
- although propofol is highly lipophilic and has a high Vd at steady-state, t_{1/2β} is comparable to t_{1/2α} such that peripheral compartments do not become saturated even with long infusions
- CSHT of propofol infusion @ 10min = 5min, @ 3hr = 9min

Monitoring of TIVA:
- when using propofol there is no ‘point of delivery’ measure of the target concentration comparable to the end-tidal monitoring of inhalational agents
- a target controlled infusion (TCI) will display a calculated value for plasma concentration based upon the software model used (Marsh or Schnider) and the information it has been given, usually patient weight and age