Pharm-10A4 Describe the time course between an intravenous injection of a general anaesthetic agent to loss of consciousness. Explain the delay using pharmacokinetic principles.

After injection of an intravenous anaesthetic agent, the following sequence of events must occur before loss of consciousness → this results in the observed delay

(1) drug reaches central compartment
(2) drug reaches blood brain barrier
(3) drug diffuses across blood brain barrier
(4) drug reaches threshold concentration at effect site
(5) drug metabolism and clearance

At the same time, as soon as the anaesthetic drug is injected, it begins to undergo redistribution, metabolism and clearance → central compartment concentration falls → slightly delays onset

(1) **Drug reaches central compartment**

Faster injection → drug enters central compartment faster → more rapid onset

Larger dose injected → more drug enters central compartment → more rapid onset

(2) **Drug reaches blood brain barrier**

Drug carried from site of injection to blood brain barrier by systemic circulation and heart ∴ delay depends on cardiac output and distance travelled

Injection closer to effect site → more rapid onset
(e.g. injection into central line faster vs peripheral cannula)

Higher cardiac output → more rapid onset

Conditions that reduce cardiac output will delay drug reaching blood brain barrier ∴
↓ rate of onset

↓ CO by old age, cardiac failure, etc
↑ CO by pregnancy, sepsis, etc

(3) **Drug diffuses across blood brain barrier**

Rate of diffusion across blood brain barrier obeys Fick law:

$$ R = \frac{sol}{\sqrt{MW}} \times \frac{Area}{thickness} \times \Delta Concentration $$

∴ rate of diffusion proportional to concentration gradient → greater concentration gradient → more rapid onset
Greater concentration gradient from:

1. Larger dose injected
2. ↓ volume of distribution → higher central compartment concentration after bolus
3. ↓ protein binding → more free drug available for diffusion across BBB
4. ↑ unionised fraction (depends on pKa of drug) → ionised drug cannot diffuse across BBB

Also ↑ lipid solubility → ↑ rate of diffusion across BBB → ↑ rate of onset

↑ permeability of BBB (e.g. during meningitis) → ↑ rate of onset

Time for effect site [drug] to equilibrate with plasma [drug] is reflected by $k_{e0}$ value

$k_{e0}$ is defined as the rate of elimination of drug from effect site, which also reflects rate of drug uptake by the effect site → this impacts on the time taken for effect site to reach equilibrium with plasma

Mathematically, $t_{1/2}k_{e0}$ is time taken for 50% equilibration between effect site and plasma $\rightarrow \ t_{1/2}k_{e0} = \ln2/k_{e0}$

∴ Smaller $k_{e0}$ → larger $t_{1/2}k_{e0} →$ effect site takes longer to equilibrate with plasma

E.g. propofol has larger $k_{e0}$ than midazolam → plasma and effect site reach equilibrium quicker for propofol than midazolam → propofol has more rapid onset than midazolam

(4) Drug reaches threshold concentration at effect site

- More potent the drug → lower concentration required to exceed threshold → ↑ rate of onset

- Having other drugs in system → synergism → lower threshold required to exert effect → more rapid onset
e.g. premedication with midazolam increases rate of onset of hypnosis after propofol bolus

(5) Drug metabolism and clearance

↑ rate of metabolism → ↑ clearance → slower rise in plasma concentration → slower for effect site to reach threshold → ↓ rate of onset

this is less important for bolus dosing of anaesthetic agent on induction as rate of metabolism usually much lower than rate of equilibration between effect site and plasma

Individual variability

Each of the above effects can vary greatly between individuals → alter rate of onset
Examiner’s comments – 60% of candidates passed this question.

The delay to loss of consciousness after intravenous injection of an induction agent is a very specific event that requires detailed knowledge of pharmacokinetics. Descriptions of the time course had to indicate that the delay involved the build up of an adequate or threshold concentration at the effect site for loss of consciousness to occur.

There were many facts that attracted marks in this question with the better answers providing fuller justifications. For example simple knowledge such as using a bolus or loading dose and injecting the dose faster attracted marks but explaining that these practices led to a higher dose of agent in the central compartment which then leads to a larger concentration gradient driving the agent into the effect site (CNS) more quickly attracted higher marks.

Similar discussions about the importance of cardiac output and pathological situations where the cardiac output may be altered, injecting into a larger vein closer to the heart instead of a peripheral vein, about smaller volume of distribution leading to a larger concentration in the central compartment (despite the paradox that a lower lipid solubility is often associated with a smaller Vd) all attracted marks. Many candidates showed an appreciation of the complexity of pharmacokinetics, describing how redistribution and metabolism begin to occur simultaneous to delivery and may slow the build up of central compartment concentration and delay onset of action to a small degree.

Diagrammatic representation of a 3 compartment pharmacokinetic model with correct descriptions with highlighting and description of the importance of the Keo also attracted marks. Comparisons of Keo”s between differing intravenous induction agents were also central to the question. Graphs depicting the change in plasma and superimposed effect site concentrations with time attracted marks, with the better graphs indicating the threshold level needed at the effect site for loss of consciousness to occur.

A discussion of the potential for speed of effect to be influenced at the neuronal membrane and by the specific molecular characteristics of the induction agent and how this related to Fick”s Law and to unionized drug was also considered relevant. Candidates often ran into difficulties with their answer if they spent too much time discussing how the effect of induction agents wore off or how they were cleared from the circulation, or spoke at length about unrelated facts concerning specific agents.