# CORE NOTE
# Introduction to Pharmacokinetics and Pharmacodynamics

Companion to the existing BAP Academy video. This note reinforces its core framework and adds clearly marked examination extensions.

### Learning objectives

- Distinguish pharmacokinetics (PK) from pharmacodynamics (PD).
- Explain absorption, distribution, metabolism and excretion (ADME) , including first-pass extraction and protein binding.
- Interpret clearance, apparent volume of distribution and elimination half-life, including simple calculations.
- Distinguish plasma concentration, effect-site concentration and clinical effect.
- Interpret basic dose–response concepts and explain why drug effects may lag behind plasma concentrations.
- Explain steady-state infusion and context-sensitive half-time.

## 1 The organising framework

Pharmacokinetics asks: What does the body do to the drug? It describes how drug amounts and concentrations change over time through absorption, distribution and elimination. Pharmacodynamics asks: What does the drug do to the body? It relates exposure at the relevant site to a defined physiological or clinical response.

The sequence is dose → plasma concentration → effect-site concentration → receptor/target interaction → observed effect. These quantities are related but are not interchangeable.

## 2 ADME: four processes, different consequences

| Process | Core concept |
|---|---|
| **Absorption** | Entry into systemic circulation; route, formulation, gut motility and first-pass extraction influence systemic exposure. |
| **Distribution** | Reversible movement between blood and tissues; plasma concentration can fall without drug being eliminated. |
| **Metabolism** | Chemical biotransformation, often hepatic; metabolites may be inactive, active or toxic. Metabolism is not excretion. |
| **Excretion** | Removal of unchanged drug or metabolites, commonly via kidneys or bile. |

Intravenous dosing has 100% systemic bioavailability by definition. Bioavailability describes the fraction reaching systemic circulation unchanged. It does not describe the *speed* of absorption: rate and extent are separate properties. Delayed gastric emptying, for example, slows the rate of absorption of most oral drugs.

**First-pass extraction** After oral administration, drug can be lost in the gut wall and liver before reaching the systemic circulation. A drug may be completely absorbed across the gut wall yet have low bioavailability because of hepatic extraction. Routes that avoid the portal circulation (sublingual, transdermal, intravenous) bypass first pass. The rectal route avoids it only partially, because the superior rectal vein drains into the portal system.

## 3 Volume of distribution (Vd) and protein binding

Apparent volume of distribution links the amount of drug in the body to its measured plasma concentration: Vd = amount in body / plasma concentration. It is a proportionality term, not an anatomical compartment. A large Vd often indicates extensive tissue distribution or binding; Vd may exceed total body water. A very small Vd (for example 0.1 L/kg, about 7 L in a 70 kg adult) suggests a drug largely confined to plasma.

Clinical interpretation: after an IV bolus, a marked early decline in plasma concentration may reflect distribution into tissues rather than elimination.

**Initial concentration after a bolus .** In a multicompartment model, the initial plasma concentration is approximately **dose / V1**, where V1 is the central compartment volume. It is not determined by the much larger terminal-phase volume. A smaller central volume (for example in low cardiac output states) gives a higher initial concentration for the same dose.

**Protein binding .** Only unbound drug is generally available for diffusion, receptor interaction and clearance by many pathways. In hypoalbuminaemia, the unbound fraction of a highly albumin-bound drug rises. Protein binding says nothing about oral bioavailability.

## 4 Clearance (CL)

Clearance is the hypothetical volume of plasma or blood cleared of drug per unit time (e.g., L/h). For a linear model: elimination rate = CL × concentration. It is not the mass of drug eliminated per minute; that mass rate depends on both clearance and concentration.

In first-order (linear) kinetics, clearance is constant. The elimination *rate* falls as concentration falls, but clearance does not. Total body clearance is the sum of the clearances of the individual eliminating organs. **Hepatic extraction: High-extraction drugs:** clearance approaches hepatic blood flow and is sensitive to perfusion. A fall in enzyme activity alone has relatively little effect. **Low-extraction drugs:** clearance depends mainly on intrinsic metabolic capacity and the unbound fraction, and is relatively insensitive to blood flow. Enzyme inhibition lowers their clearance; enzyme induction raises it.

## 5 Half-life and elimination kinetics

For a one-compartment model with linear elimination: t½ = 0.693 × Vd / CL. Thus half-life becomes longer if Vd rises while CL stays constant, or if CL falls while Vd stays constant. If both change, consider the ratio: doubling Vd while halving CL gives four times the half-

life. This relationship is a model-specific approximation; multicompartment drugs have several exponential phases.

First-order elimination removes a constant fraction per unit time. After 1, 2, 3 and 4 half-lives, 50%, 25%, 12.5% and 6.25% of the drug remains. Capacity-limited (approximately zero-order) elimination removes an approximately constant amount per unit time over the saturated range. In that range the time to halve the concentration is not constant and lengthens as the concentration rises, so half-life depends on dose. Do not equate terminal half-life with duration of clinical effect after a single bolus. Offset after a bolus is often governed by redistribution.

## 6 Plasma concentration versus effect-site concentration

Following a rapid IV bolus, plasma concentration rises before the effect-site concentration has equilibrated. The effect may therefore peak after plasma concentration has already started to decline. This delay is commonly described using an effect compartment and an equilibration rate constant (ke0). The equilibration half-time is **t½ke0 = 0.693 / ke0**, so a larger ke0 means faster equilibration. The effect compartment is a model construct that receives negligible drug mass. Effect-site concentration is derived from the model; it is not measured directly in patients.

A concentration–effect plot may show hysteresis when plasma concentration is used as a surrogate for effect-site exposure. With effect on the y-axis and plasma concentration on the x-axis, points joined in time order trace a *counterclockwise* loop when effect lags plasma. The direction reverses if the axes are swapped. The loop collapses to a single curve when effect is plotted against effect-site concentration.The observed effect also depends on receptor sensitivity and the chosen clinical endpoint.

Because of this delay, redosing before the effect-site peak has been reached can lead to overshoot, as the earlier dose is still equilibrating.

## 7 Pharmacodynamics and receptor concepts

An agonist activates a receptor; an antagonist prevents or reduces activation. A partial agonist has a lower maximal intrinsic effect than a full agonist in the same system. A reversible competitive antagonist typically shifts an agonist concentration–response curve to the right without necessarily reducing its maximal response, whereas insurmountable antagonism may reduce the maximum.

Potency concerns the concentration or dose required to produce a specified effect (often EC50); efficacy concerns the maximal effect achievable (Emax). Greater potency does not necessarily mean greater maximal efficacy or clinical safety. The two vary independently.

In a graded (single-individual) Emax model, **EC50 is the concentration producing 50% of the maximal effect.** In a quantal (population) analysis the corresponding quantity is the ED50 or EC50 for response in 50% of patients; do not mix the two.

The sigmoid Emax model is: **E = Emax × C^γ / (C50^γ + C^γ)**, where γ is the Hill coefficient. With γ = 1, E/Emax = C / (C + EC50). For example, at C = 4 × EC50, E/Emax = 4/5 = 80%. A Hill coefficient greater than 1 makes the curve steeper.

## 8 Infusions and context-sensitive half-time

During infusion, distribution compartments accumulate drug. After stopping the infusion, drug can redistribute back into plasma.

**Context-sensitive half-time** is the time required for plasma concentration to fall by 50% after stopping an infusion that has been maintained to hold a constant plasma concentration, where the "context" is the duration of that infusion. It differs from terminal elimination half-life and varies markedly among drugs. A drug with a longer terminal half-life does not necessarily have a longer context-sensitive half-time at a given infusion duration. Remifentanil's context-sensitive half-time remains short even after prolonged infusion, because of rapid metabolism by non-specific esterases.

Context-sensitive half-time refers to the *plasma* concentration. It should not be confused with the time for effect-site concentration to fall.

**Steady state.** For a linear model, at steady state the input equals the output, so **infusion rate = CL × Css**, or **Css = infusion rate / CL.** The maintenance infusion rate needed for a target concentration is therefore approximately target concentration × clearance. A fall in clearance raises Css for a fixed rate and, if Vd is unchanged, lengthens the half-life, so the new steady state is reached more slowly. Reaching a target concentration promptly may require a loading strategy; clinical titration remains essential.

## 9 Worked example

Assume a one-compartment drug has Vd = 40 L and CL = 4 L/h. Then t½ = 0.693 × 40/4 = 6.93 h. If clearance falls to 2 L/h with Vd unchanged, t½ increases to 13.86 h.

A drug is infused at 6 mg/min with CL = 1.5 L/min. Css = 6 / 1.5 = 4 mg/L. If clearance falls to 1.0 L/min with the rate unchanged, Css = 6 / 1.0 = 6 mg/L. With Vd unchanged, t½ also lengthens, so the new steady state is approached more slowly.

These examples illustrates the mathematical relationship; real anaesthetic drugs may

show multicompartment kinetics.

## 10 Common EDAIC pitfalls

- Distribution is not the same as elimination.
- Metabolism is not excretion.
- Clearance (volume/time) is not elimination rate (mass/time).
- Apparent Vd is not necessarily a real physiological volume.
- Rate of absorption is not extent of absorption (bioavailability).
- Terminal half-life does not by itself predict awakening after a short infusion or bolus.
- Plasma and effect-site concentrations may differ substantially during rapid concentration changes.
- Competitive antagonists shift the curve; they do not necessarily lower the maximum.
- Potency, efficacy and therapeutic safety are different properties.

## 11 Self-check

**1. Why can plasma concentration decline immediately after an IV bolus without much drug being eliminated?** Drug redistributes from the central compartment into peripheral tissues, which lowers the plasma concentration while total body drug is unchanged.

**2. What happens to elimination half-life if clearance halves and Vd stays constant?** It doubles ($t½ = 0.693 \times Vd / CL$).

**3. Why can clinical effect lag behind plasma concentration?** The effect site equilibrates with plasma with a delay, described by ke0. Effect follows the effect-site concentration, which peaks after the plasma peak.

**4. How do competitive antagonism and partial agonism differ?** A competitive reversible antagonist has no intrinsic activity and shifts the agonist curve to the right with the same maximum. A partial agonist activates the receptor but with lower maximal effect, even at full occupancy.

**5. Why does infusion duration matter when interpreting recovery after stopping an anaesthetic?** Peripheral compartments fill during a longer infusion, so more drug returns to plasma afterwards and the context-sensitive half-time can lengthen. The size of this effect varies between drugs.

**6. A drug is infused at 12 mg/min with CL = 3 L/min. What is Css?** $Css = 12 / 3 = 4$ mg/L.

**7. After a bolus, effect is plotted against plasma concentration and the points form a loop. What does it indicate?** Hysteresis, meaning a delay between plasma concentration and effect. The loop collapses when effect is plotted against effect-site concentration.