

Unit 3: Pharmacokinetics

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3.1 Basic considerations: describing what the body does to the drug

Pharmacokinetics is the quantitative study of ADME: absorption, distribution, metabolism and excretion of a drug, followed through its concentration in the body over time. In practice the concentration is measured in plasma (or blood or serum), because plasma can be sampled repeatedly and, for most drugs, tracks the concentration at the site of action with a short delay. Plotting plasma concentration against time gives the **plasma level time curve**, and this unit extracts standard parameters from that curve and uses them to design dosage regimens.

The parameters used throughout the unit, each defined once here:

- **C_{max}**: the peak plasma concentration after a dose.
- **T_{max}**: the time at which C_{max} occurs; a measure of the rate of absorption.
- **AUC**: the area under the plasma concentration time curve (concentration x time, for example mg·h/L); the measure of total drug exposure.
- **C₀**: the concentration at time zero obtained by extrapolating the curve after an intravenous bolus; used to calculate V_d.
- **K (also written K_e or k_{el})**: the overall elimination rate constant (per hour); the fraction of drug in the body eliminated per unit time.
- **Half life (t_{1/2})**: the time for plasma concentration (or amount) to fall by half; for first order elimination, $t_{1/2} = 0.693 / K$.
- **Volume of distribution (V_d)**: the apparent volume that would contain the total amount of drug in the body at the measured plasma concentration: $V_d = \text{amount in body} / \text{plasma concentration}$. A proportionality constant, not a real anatomical volume; a large V_d means extensive tissue distribution.
- **Clearance (CL)**: the volume of plasma cleared of drug per unit time (for example L/h); $CL = K \times V_d$, and for an intravenous dose $CL = \text{Dose} / AUC$.
- **Bioavailability (F)**: the fraction of the administered dose that reaches the systemic circulation unchanged; Unit 4 is devoted to it.

Two kinetic orders govern almost everything. In **first order** (linear) kinetics, a constant fraction of drug is eliminated per unit time: K and half life are constant, and AUC rises in proportion to dose. In **zero order** kinetics, a constant amount is eliminated per unit time because the eliminating machinery is saturated; ethanol is the familiar example, and section 3.8 treats saturable elimination properly. Most drugs at therapeutic doses follow first order kinetics, so the models of sections 3.3 to 3.6 are built on first order rate constants.

3.2 Pharmacokinetic models

A model is a mathematical picture of the body simple enough to calculate with and realistic enough to predict. Three families are used:

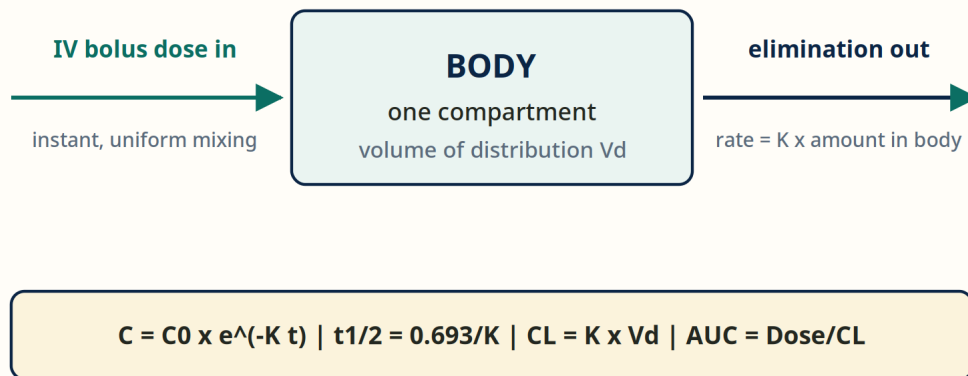
- **Compartment models**. The body is represented as one or more compartments: not real organs, but volumes in which the drug is assumed to mix instantly and uniformly, connected by first order transfer

rate constants. The mammillary model, a central compartment (blood and well perfused tissues) connected to peripheral compartments (poorly perfused tissues), is the standard picture. Sections 3.3 to 3.6 develop these.

- **Physiological (flow) models.** Compartments correspond to real organs with real blood flows and tissue partition coefficients. They predict real tissue concentrations and scale between species, but need much measured data and are research tools, not this subject's working model.
- **Model independent description.** AUC, Cmax, Tmax and half life read directly from the measured curve without assuming a compartment structure; this is how bioequivalence data (Unit 4) are compared, since the comparison must not depend on a model being right.

3.3 The one compartment model: intravenous bolus

The One Compartment Model (IV Bolus)



Log plasma concentration falls on one straight line with slope minus K

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Figure: The simplest useful picture of the body: one instantly mixing volume, one first order exit. The log concentration plot is a straight line whose slope is minus K, the single most used graphical method in pharmacokinetics.

The one compartment open model treats the body as a single volume V_d into which an intravenous bolus is injected and mixes instantly, giving $C_0 = \text{Dose} / V_d$, and from which drug is eliminated by a first order process with rate constant K . The concentration at time t is:

$$C = C_0 \times e^{(-K t)}$$

Taking logarithms gives $\log C = \log C_0 - (K / 2.303) \times t$, so a plot of log concentration against time is a straight line: the slope gives K , the intercept gives C_0 , and from these every other parameter follows: $t_{1/2} = 0.693 / K$, $V_d = \text{Dose} / C_0$, $AUC = C_0 / K$ (the total area from zero to infinity), and $CL = K \times V_d = \text{Dose} / AUC$.

Worked example. A 1000 mg intravenous bolus gives an extrapolated C_0 of 50 mg/L and, from the log plot slope, $K = 0.15$ per hour.

- $V_d = \text{Dose} / C_0 = 1000 / 50 = 20 \text{ L}$.
- $t_{1/2} = 0.693 / 0.15 = 4.62 \text{ hours}$.
- $AUC = C_0 / K = 50 / 0.15 = 333 \text{ mg}\cdot\text{h/L}$.

- $CL = \text{Dose} / AUC = 1000 / 333 = 3.0 \text{ L/h}$. Check: $K \times V_d = 0.15 \times 20 = 3.0 \text{ L/h}$. The two routes to clearance agree, as they must.
- Concentration at 6 hours: $C = 50 \times e^{(-0.15 \times 6)} = 50 \times e^{(-0.9)} = 50 \times 0.407 = 20.3 \text{ mg/L}$.

This calculation is the foundation of dose work: a loading dose is target $C \times V_d$, and maintenance requirements are set by clearance.

3.4 The one compartment model: intravenous infusion

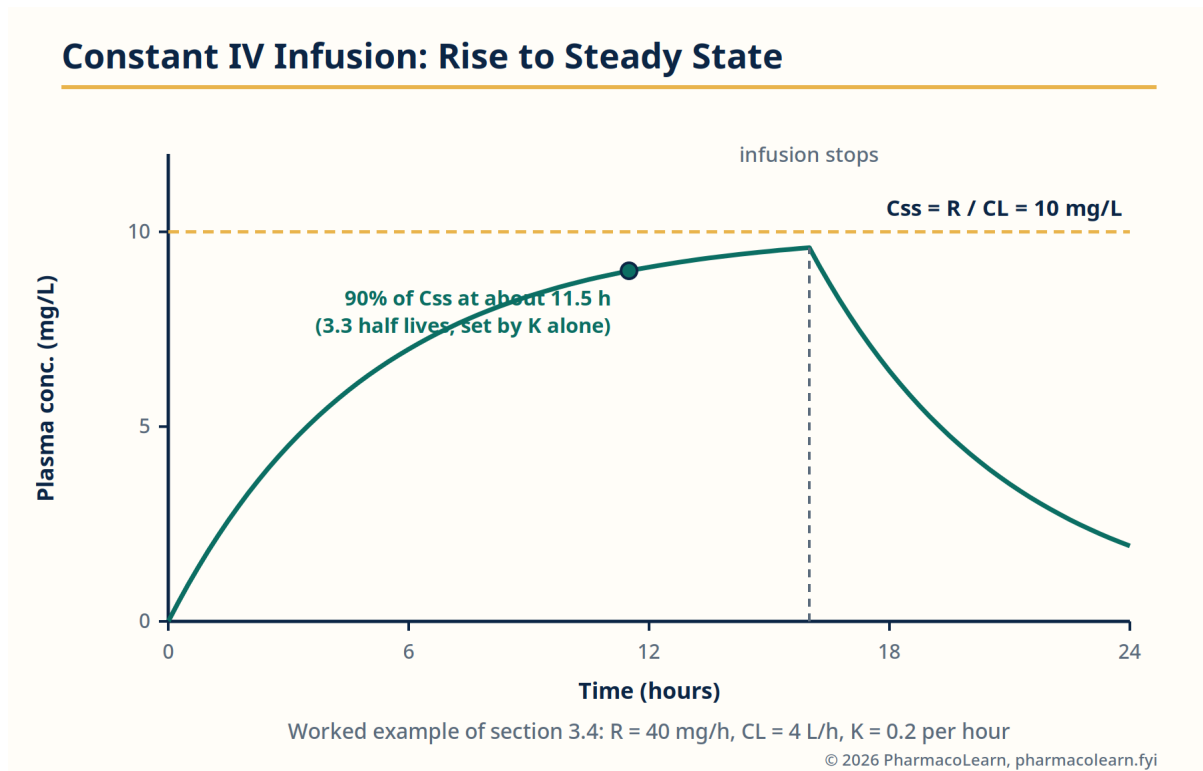


Figure: An infusion adds drug at a constant rate while elimination removes it in proportion to concentration. The two balance at the steady state, C_{ss} , and the half life alone decides how long the approach takes.

With a constant infusion rate R (amount per unit time) into the one compartment model, drug enters at a constant rate and leaves at a rate proportional to concentration, so concentration rises and levels off when input and output are equal. During the infusion:

$$C = (R / CL) \times (1 - e^{(-K t)})$$

The plateau value is the **steady state concentration**, $C_{ss} = R / CL$. Its decisive properties are examination favourites: C_{ss} depends only on the infusion rate and the clearance, not on V_d ; but the time to reach the plateau is set by the half life alone, about 50 percent of C_{ss} in one half life, 90 percent in 3.32 half lives, and practical steady state in 4 to 5 half lives. Changing the infusion rate changes the plateau but not the time taken to reach it. When the infusion stops, the concentration falls exponentially with the same K , from C_{ss} .

If the plateau must be reached immediately, a **loading dose** comes first: $LD = C_{ss} \times V_d$ fills the volume to the target concentration at once, after which the infusion replaces what elimination removes.

Worked example. A drug with $K = 0.2 \text{ per hour}$ and $V_d = 20 \text{ L}$ (so $CL = K \times V_d = 4 \text{ L/h}$) is infused at $R = 40 \text{ mg/h}$.

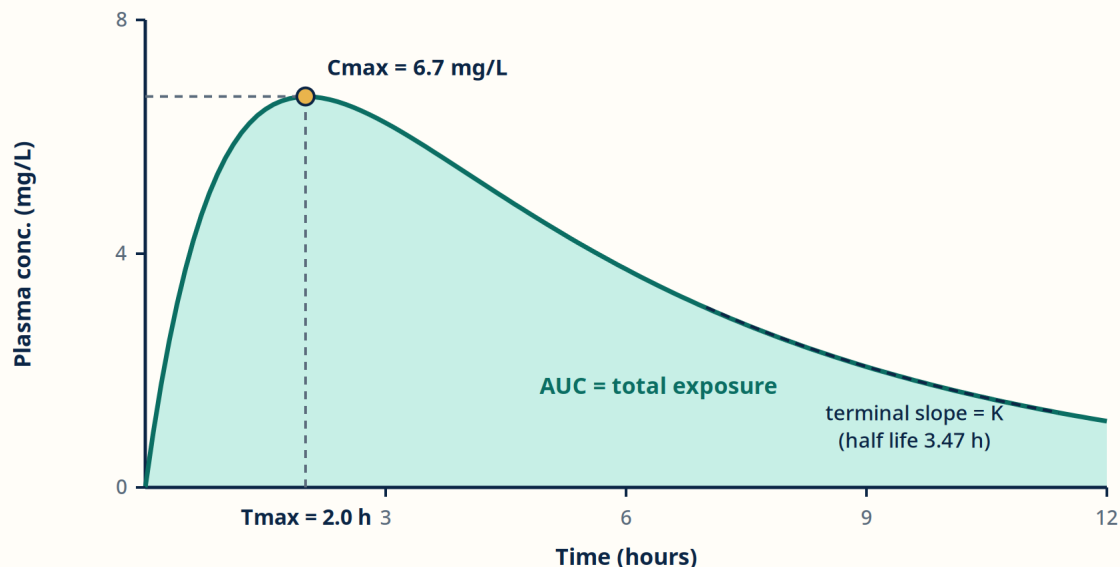
- $C_{ss} = R / CL = 40 / 4 = 10 \text{ mg/L}$.
- $t_{1/2} = 0.693 / 0.2 = 3.47 \text{ hours}$, so the infusion reaches 90 percent of C_{ss} after 3.32×3.47 , about 11.5 hours, and practical steady state in about 14 to 17 hours.

- Loading dose for an immediate 10 mg/L: $LD = 10 \times 20 = 200$ mg.
- Doubling the infusion to 80 mg/h doubles C_{ss} to 20 mg/L, but it still takes the same 11.5 hours to reach 90 percent of the new plateau.

This separation, clearance sets the level and half life sets the timing, also governs repeated oral dosing, where the average steady state concentration is $C_{ss,avg} = (F \times \text{Dose}) / (CL \times \text{dosing interval})$.

3.5 The one compartment model: extravascular administration

Extravascular (Oral) Dose: C_{max} , T_{max} and AUC



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Figure: After an oral dose the curve is the sum of two exponentials: absorption pushing concentration up, elimination pulling it down. C_{max} and T_{max} sit at the balance point; the terminal slope gives K and the back extrapolated line gives the absorption rate constant k_a .

After an oral (extravascular) dose, drug must be absorbed before it can be eliminated, and the concentration reflects both processes at once. With first order absorption (rate constant k_a) and first order elimination (K), the one compartment equation is:

$$C = [F \times \text{Dose} \times k_a / (V_d \times (k_a - K))] \times (e^{(-K t)} - e^{(-k_a t)})$$

where F is the fraction absorbed intact (bioavailability). The curve rises while absorption outruns elimination, peaks at C_{max} when the two rates are momentarily equal, then declines. T_{max} depends on both rate constants:

$$T_{max} = \ln(k_a / K) / (k_a - K)$$

The terminal (log linear) part of the curve has slope minus K , provided absorption has finished; extrapolating this line back and subtracting it from the measured concentrations (the **method of residuals**, or feathering) gives a second straight line whose slope is minus k_a . One caution governs interpretation: the terminal slope reflects the slower of the two processes. Normally k_a exceeds K and the terminal slope is K ; but if absorption is slower than elimination (k_a less than K), as with sustained release products, the terminal slope measures k_a instead, the **flip-flop** situation, and a naive reading reports the absorption half life as if it were the elimination half life.

Worked example. A 100 mg oral dose, $F = 1$, $V_d = 10$ L, $k_a = 1.0$ per hour, $K = 0.2$ per hour.

- The coefficient $F \times \text{Dose} \times k_a / (V_d \times (k_a - K)) = (1 \times 100 \times 1.0) / (10 \times 0.8) = 12.5 \text{ mg/L}$.
- $T_{\max} = \ln(1.0 / 0.2) / (1.0 - 0.2) = \ln 5 / 0.8 = 1.609 / 0.8 = 2.0 \text{ hours}$.
- $C_{\max} = 12.5 \times (e^{-(0.2 \times 2.0)} - e^{-(1.0 \times 2.0)}) = 12.5 \times (0.670 - 0.135) = 12.5 \times 0.535 = 6.7 \text{ mg/L}$.
- $AUC = F \times \text{Dose} / CL$, with $CL = K \times V_d = 0.2 \times 10 = 2 \text{ L/h}$, so $AUC = 100 / 2 = 50 \text{ mg}\cdot\text{h/L}$. (AUC is independent of k_a : k_a decides the shape of the curve, not its area.)

A lag time before absorption begins (gastric emptying, tablet disintegration) shifts the whole curve to the right by that amount.

3.6 The multi compartment model: the two compartment model in brief

Many drugs, after an intravenous bolus, give a log concentration plot that falls steeply at first and then settles into a shallower straight line. The body is then described as two compartments: a central compartment (plasma and highly perfused tissues) receiving the dose and eliminating, and a peripheral compartment (poorly perfused tissues) exchanging drug with it by distribution. The concentration follows a biexponential equation:

$$C = A \times e^{(-\alpha t)} + B \times e^{(-\beta t)}$$

The first, steep phase is the **distribution (alpha) phase**, during which drug is both distributing and being eliminated; the second, shallow phase is the **terminal (beta) phase**, in which distribution equilibrium has been reached and the decline reflects elimination alone. Terminal half life is $0.693 / \beta$; $AUC = A/\alpha + B/\beta$; clearance is still Dose / AUC .

Worked example, read off a plot. A drug fits $A = 30 \text{ mg/L}$, $\alpha = 1.2 \text{ per hour}$, $B = 10 \text{ mg/L}$, $\beta = 0.1 \text{ per hour}$. The terminal half life is $0.693 / 0.1 = 6.93 \text{ hours}$, and $AUC = 30/1.2 + 10/0.1 = 25 + 100 = 125 \text{ mg}\cdot\text{h/L}$. Note how the slow terminal phase, though it starts at only 10 mg/L , contributes 100 of the 125 units of area: for two compartment drugs the terminal phase dominates exposure, and sampling stopped during the distribution phase badly underestimates AUC and half life.

3.7 Nonlinear pharmacokinetics: causes

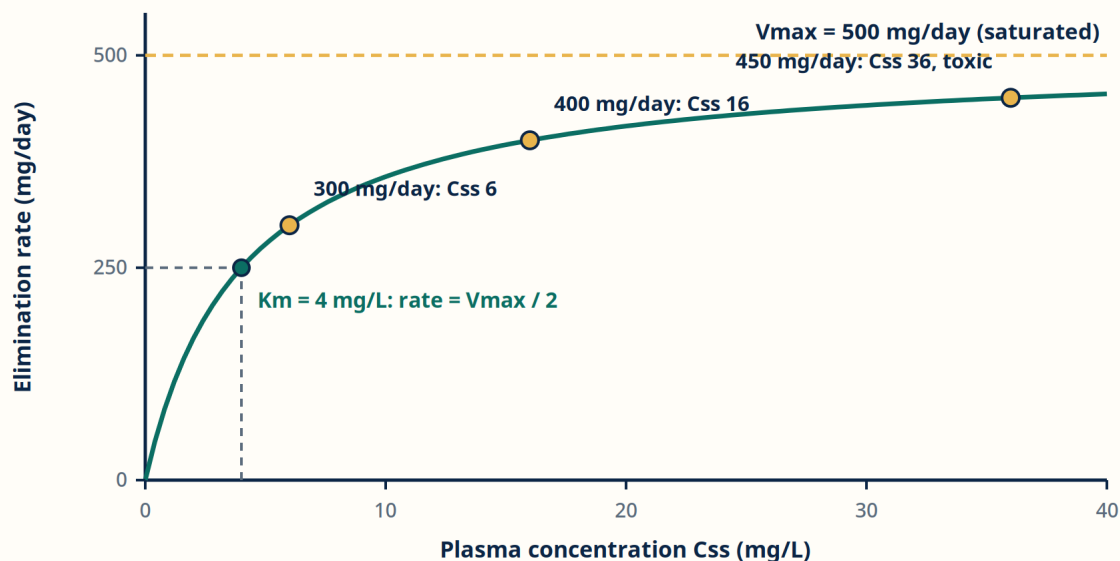
Linear kinetics assumes the machinery of elimination has unlimited capacity. When a process saturates, kinetics become nonlinear: parameters change with dose, AUC rises more than proportionally, and half life lengthens as concentration rises. The causes are:

- **Saturable metabolism:** the metabolising enzyme is at capacity; phenytoin is the classic drug, salicylates and theophylline behave similarly at high doses.
- **Saturable plasma protein binding:** as dose rises the binding sites fill, the free fraction rises, and distribution and clearance change (valproic acid, disopyramide).
- **Saturable tissue binding and saturable transport:** uptake, secretion and reabsorption transporters in gut, liver and kidney can each saturate.
- **Saturable absorption and first pass:** carriers saturating at high dose, and a first pass effect that saturates so bioavailability itself rises with dose (propranolol).
- **Time dependent changes:** autoinduction (carbamazepine speeds its own metabolism over the first weeks) and autoinhibition change parameters with time rather than dose.

The practical warning is constant: with a nonlinear drug, a small dose increase can produce a disproportionate, sometimes toxic, rise in concentration, so adjustments must be small and guided by measured levels.

3.8 The Michaelis-Menten equation and the estimation of Km and Vmax

Michaelis-Menten (Saturable) Elimination



Phenytoin of section 3.8: near saturation, small dose rises give large C_{ss} rises

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Figure: Saturable elimination in one curve. Well below K_m the process is effectively first order; well above K_m it is zero order at V_{max}; near K_m, where phenytoin is dosed, small changes have large effects.

Saturable elimination is described by the Michaelis-Menten equation, borrowed from enzyme kinetics. The rate is:

$$\text{Rate of elimination} = -dC/dt = (V_{\max} \times C) / (K_m + C)$$

where V_{max} is the maximum rate of elimination when the enzymes are saturated and K_m, the Michaelis constant, is the concentration at which the rate is half of V_{max}. Read the equation at its limits: when C is much less than K_m, the rate is approximately (V_{max} / K_m) × C, first order with an effective rate constant V_{max} / K_m; when C is much greater than K_m, the rate is approximately V_{max}, zero order; in between, the kinetics are mixed order, which is where therapeutic concentrations of phenytoin sit.

At steady state during regular dosing, the dosing rate R equals the elimination rate, so $R = V_{\max} \times C_{ss} / (K_m + C_{ss})$, which rearranges to:

$$C_{ss} = (K_m \times R) / (V_{\max} - R)$$

Worked example, phenytoin. Take V_{max} = 500 mg/day and K_m = 4 mg/L (values typical of an adult patient). At a dosing rate of 300 mg/day, $C_{ss} = (4 \times 300) / (500 - 300) = 1200 / 200 = 6$ mg/L. Raise the dose to 400 mg/day: $C_{ss} = (4 \times 400) / (500 - 400) = 1600 / 100 = 16$ mg/L. Raise it to 450 mg/day: $C_{ss} = (4 \times 450) / (500 - 450) = 1800 / 50 = 36$ mg/L, well into the toxic range. A 33 percent dose increase (300 to 400) nearly trebled the concentration, and a further 12.5 percent increase (400 to 450) more than doubled it again. As R approaches V_{max} the denominator approaches zero and C_{ss} climbs without limit: no steady state exists at or above V_{max}, and the drug accumulates indefinitely. This is why phenytoin is dosed in small increments (25 to 30 mg) near target levels, with plasma level monitoring.

Estimating K_m and V_{max} for a patient. Measure the steady state concentrations at two different dosing rates, R₁ with C_{ss1} and R₂ with C_{ss2}. Rearranging the steady state equation gives $1/R = (K_m / V_{\max}) \times (1/C_{ss}) + 1/V_{\max}$, so a plot of 1/R against 1/C_{ss} is a straight line with intercept 1/V_{max} and slope

K_m/V_{max} : from two patient points the line, and hence both parameters, can be calculated, and the dosing rate for any target C_{ss} follows. Direct and Ludden plots are alternative graphical forms of the same algebra. Two points are a minimum, and predictions are checked against the next measured level.

3.9 Drug interactions: introduction and protein binding interactions

A drug interaction is a change in the effect or blood level of one drug caused by another drug (or food, or a herbal product), through pharmacokinetic mechanisms (absorption, distribution, metabolism, excretion, this section) or pharmacodynamic mechanisms (effects adding or opposing at the site of action, Unit 5).

Pharmacokinetic interactions matter most when the affected drug has a narrow therapeutic index, a steep concentration response curve, or nonlinear kinetics, the phenytoin of section 3.8 being sensitive on all three counts.

Protein binding interactions. Only unbound (free) drug crosses membranes, acts, and is available for metabolism and excretion, so the free concentration is the working concentration. When two highly bound drugs compete for the same sites on albumin (or alpha 1 acid glycoprotein, which binds many basic drugs), one can displace the other and transiently raise its free concentration: the classic example is a sulfonamide or phenylbutazone displacing warfarin or tolbutamide. The rise is usually temporary, because the freed drug is also more available for clearance, and total concentration falls until the free concentration is close to its former value. It becomes clinically important when the displaced drug has a small V_d and a narrow therapeutic index, and it is a trap in interpretation: the measured total level falls while the free (active) level is unchanged, so dosing up against the total level can poison the patient.

3.10 Tissue binding interactions

Drug bound in tissues is in equilibrium with drug in plasma, and a second drug competing for tissue binding sites can shift drug back into plasma, changing both its concentration and its volume of distribution. The standard example is digoxin: quinidine displaces digoxin from binding sites in skeletal muscle (and also reduces its renal clearance), so the digoxin plasma concentration roughly doubles while the total amount in the body changes much less, so the digoxin dose must be reduced when quinidine starts.

3.11 Cytochrome P450 based drug interactions

Most oxidative drug metabolism runs through the cytochrome P450 (CYP) enzymes of liver and gut wall, isoforms with distinct substrate lists: CYP3A4 metabolises the largest share of marketed drugs, with CYP2D6, CYP2C9, CYP2C19, CYP1A2 and CYP2E1 covering most of the rest. Interactions occur by two opposite mechanisms:

- **Enzyme inhibition.** An inhibitor slows the metabolism of every substrate of that isoform, raising their concentrations. Inhibition begins with the first dose of the inhibitor: ketoconazole and itraconazole, macrolides such as erythromycin and clarithromycin, ritonavir, cimetidine and grapefruit juice (an intestinal CYP3A4 inhibitor) all raise the levels of CYP3A4 substrates such as simvastatin and ciclosporin. Some inhibitors act by mechanism based inactivation, destroying the enzyme, so the effect outlasts the inhibitor itself.
- **Enzyme induction.** An inducer increases the amount of enzyme (and often of transporters), speeding metabolism and lowering substrate concentrations over days to weeks as new enzyme is synthesised. Rifampicin is the most potent clinical inducer, with carbamazepine, phenytoin, phenobarbital and St John's wort also important; victim drugs include oral contraceptives, warfarin, ciclosporin and many antiretrovirals, whose failure through induction can mean contraceptive failure, transplant rejection or viral resistance. When the inducer is stopped, enzyme levels fall back over a similar period and doses must be re-adjusted.

3.12 Drug interactions linked to transporters

The transporters of Unit 1 section 1.2 are interaction sites in the gut, liver and kidney. **P-glycoprotein** in the intestinal wall limits absorption of its substrates; inhibitors (verapamil, quinidine, ritonavir, ciclosporin) raise the absorption and plasma levels of substrates such as digoxin, while inducers (rifampicin) lower them.

Uptake transporters carry substrates into organs: the hepatic OATP transporters take up statins into the liver, and their inhibition by ciclosporin raises statin levels and muscle toxicity risk; renal organic anion and cation transporters (OAT, OCT) secrete drugs into urine, and competition there is the oldest transporter interaction in the subject: probenecid blocks tubular secretion of penicillin, deliberately prolonging its action, and also slows methotrexate excretion, raising its toxicity. **Renal handling** completes the list: drugs that change urinary pH change reabsorption of ionisable drugs by the ion trapping logic of section 1.3, and drugs reducing renal blood flow or filtration (NSAIDs in susceptible patients) reduce clearance of renally eliminated drugs such as lithium and digoxin.

One compartment kinetics at a glance

IV bolus: $C = C_0 e^{-K t}$; K from log plot; $V_d = \text{Dose}/C_0$; $CL = K \times V_d$

IV infusion: $C_{ss} = R / CL$; plateau in 4 to 5 half lives; $LD = C_{ss} \times V_d$

Extravascular: C from $(e^{-K t} - e^{-k_a t})$; $T_{max} = \ln(k_a/K)/(k_a - K)$

Two compartment: $C = A e^{-\alpha t} + B e^{-\beta t}$; terminal $t_{1/2} = 0.693/\beta$

Nonlinear: $\text{rate} = V_{max} \times C / (K_m + C)$; $C_{ss} = K_m \times R / (V_{max} - R)$

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