Pharmacokinetics

Part IV: Models in Pharmacokinetics

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Pharmacokinetics modeling

aims: to establish a model that accurately relates the plasma drug concentration to the rates of drug absorption, distribution, and elimination.

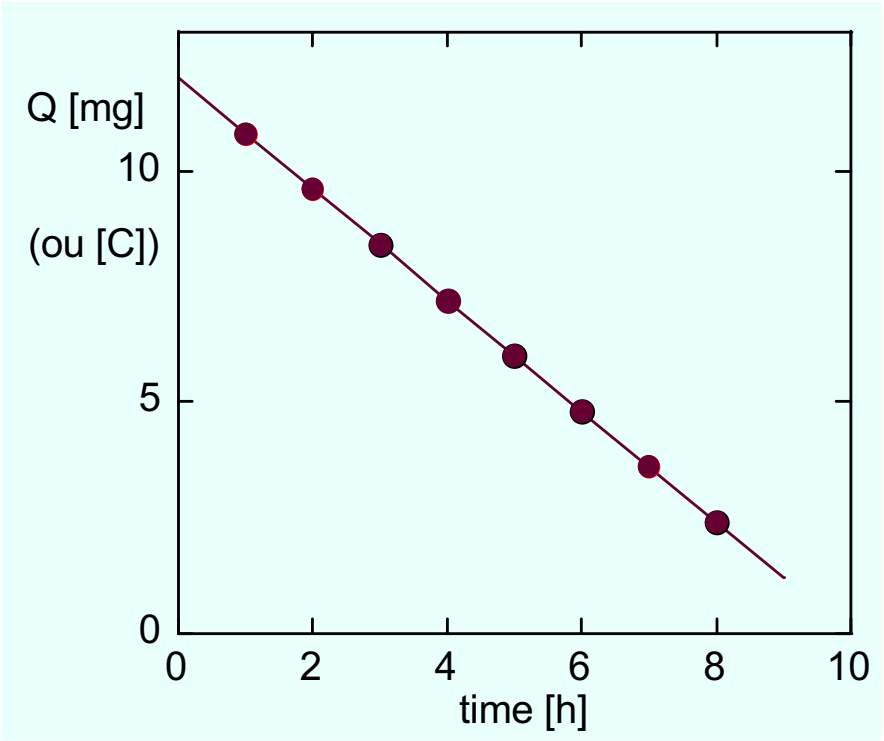
- absorption and elimination modeling:
  - zero-order kinetics
  - first-order kinetics
- drug distribution modeling:
  - single compartment models
  - multiple compartment models

models = limitations → clinical validation

Basic concepts of PK: zero-order kinetics

A zero-order process proceeds at a constant rate independent of the amount of drug presented for processing ($V = V_{max}$).

- It reflects the rate at which processes of drug interaction with membranes, carrier proteins and enzymes occur
- When drug concentrations approach the value at which the process is working at full capacity, the process will become saturated.



Saturation (zero-order): C>>Km

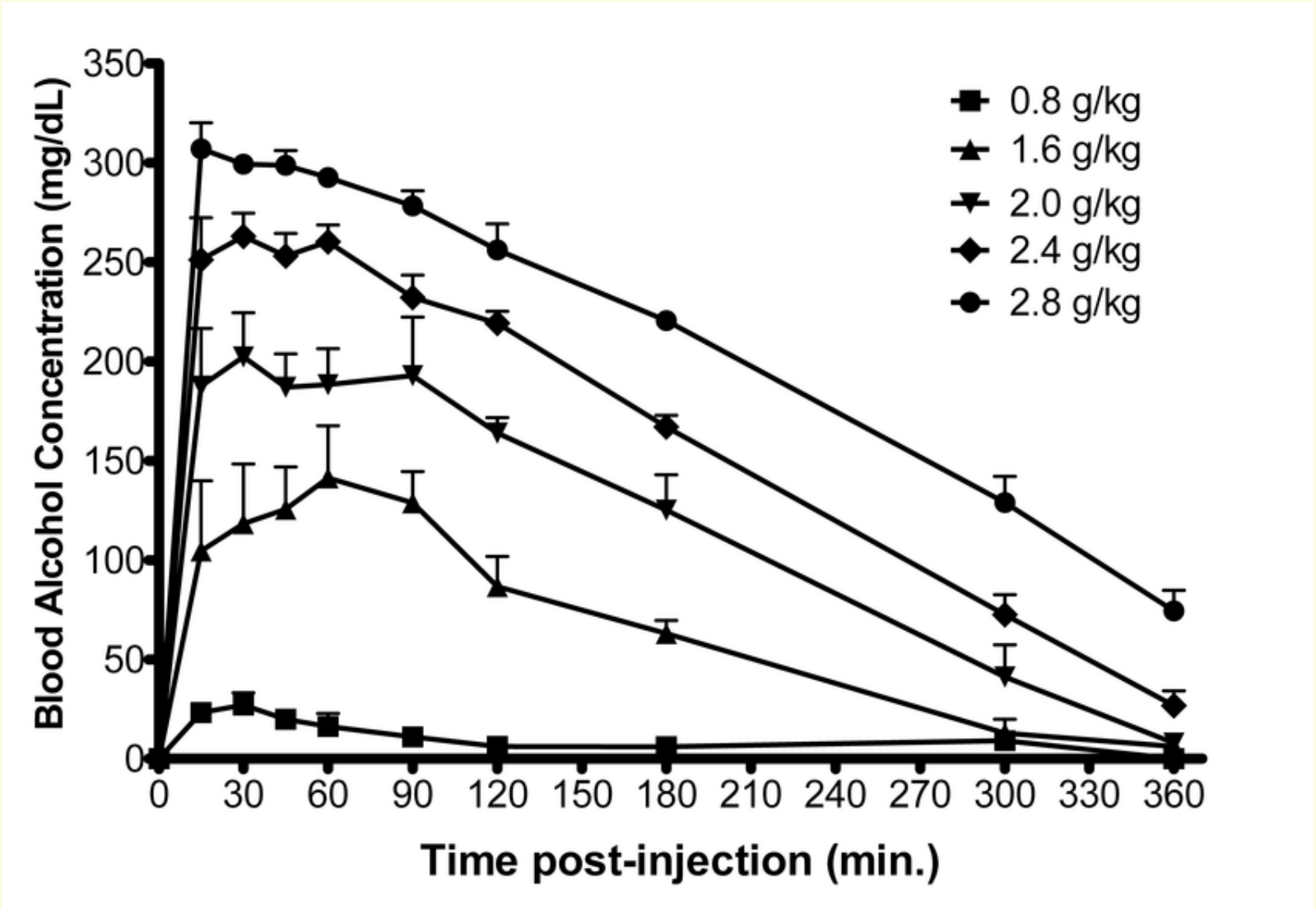
$$V = \frac{Vmax \cdot C}{Km + C} \qquad V = Vmax$$

Zero-order drug elimination kinetics:

$$c(t) = c_0 - k \times t \qquad (k=slope)$$

Examples of drugs with zero-order elimination kinetics include phenytoin, aspirin and alcohol (rare).

zero-order kinetics: alcohol



Lam, 2010

Basic concepts of PK: first-order kinetics

A first-order process: the rate is not constant, and the rate is proportional to the amount of drug undergoing the process. i.e. elimination rate is proportional to drug concentration. The concentration time-plot is curvilinear, but the logarithm of the concentration plotted against time is linear (semi-logarithmic scale). Most kinetic process affecting drug disposition in therapeutic practice is of first order.

First-order kinetics (C<<Km):

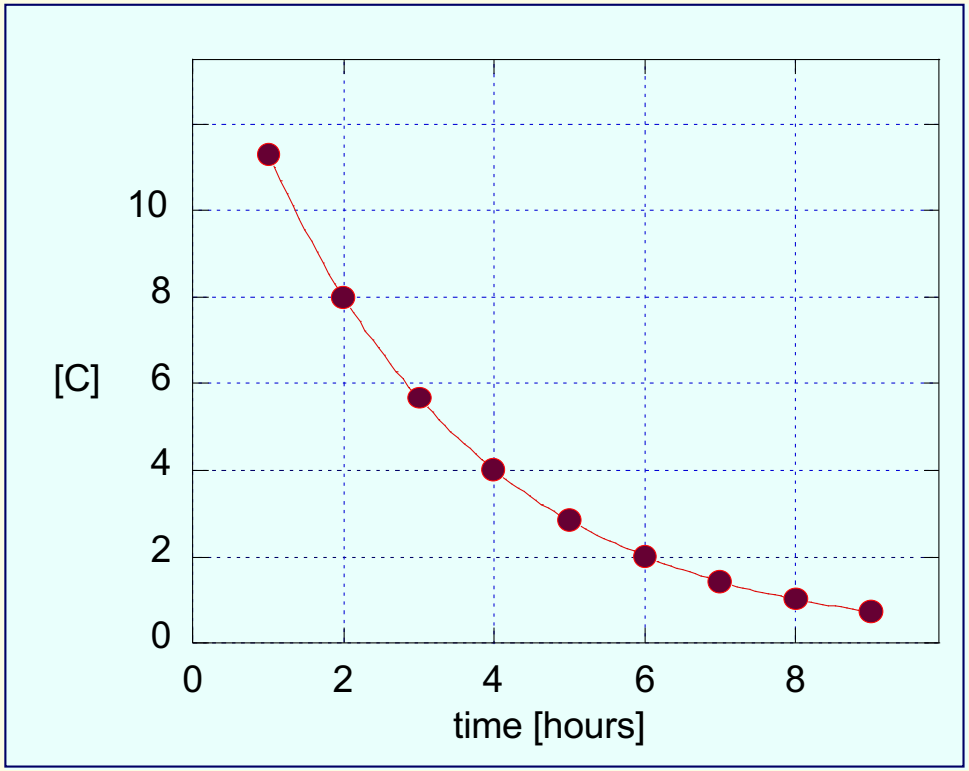
$$V = \frac{Vmax \cdot C}{Km + \cancel{C}} \qquad V = \frac{Vmax}{Km} C \qquad \frac{dC}{dt} = -k_{el}C$$

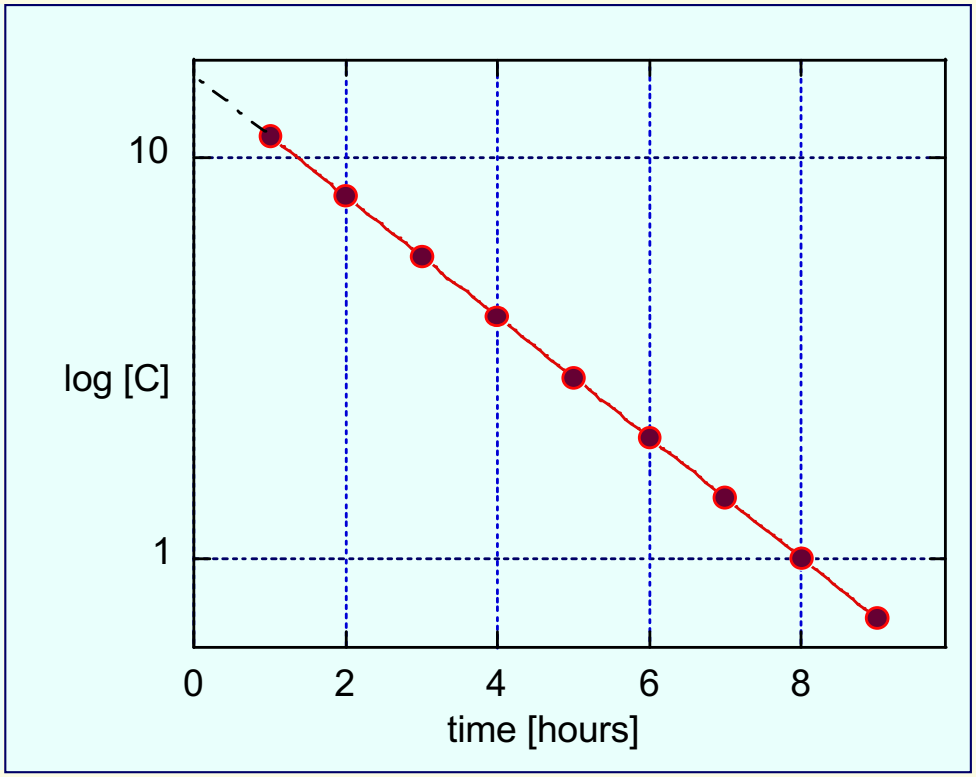
$$\frac{dC}{C} = -k_{el}dt \qquad \int_{C_0}^{C(t)} \frac{dC}{C} = -k_{el}\int_{t=0}^{t} dt \qquad \ln \frac{C}{C_0} = -k_{el}t$$

$$C(t) = C_0 e^{-k_{el}t}$$

Basic concepts of PK: first-order kinetics

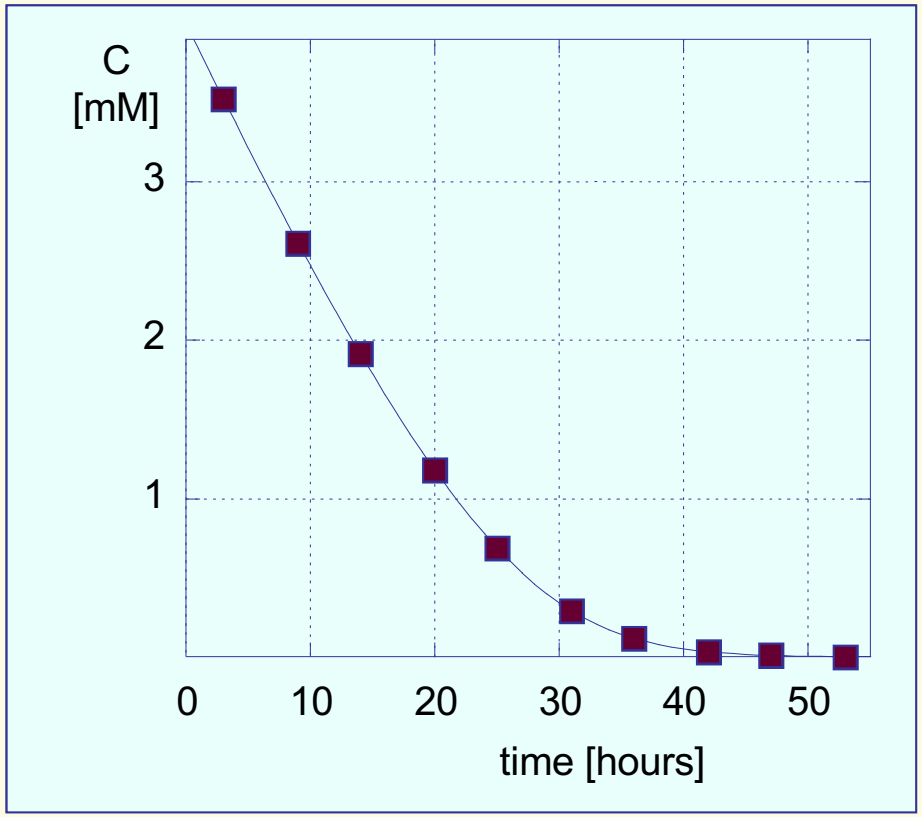
$$C(t) = C_0 e^{-k_{el}t} \qquad \ln C(t) = \ln C_0 - k_{el}t$$

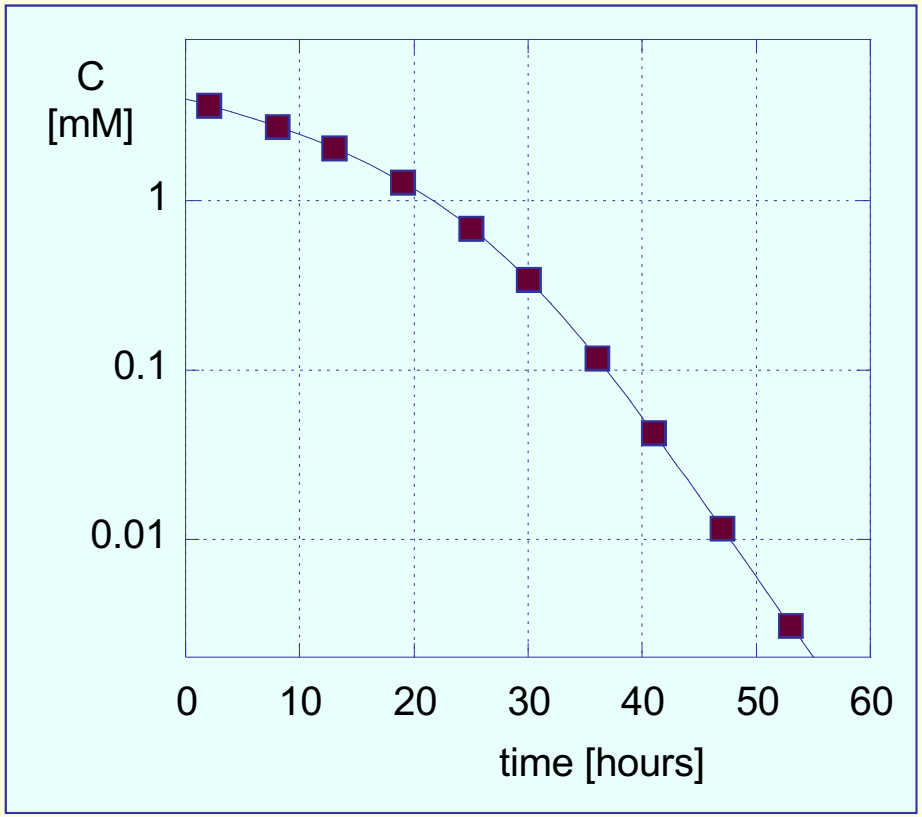




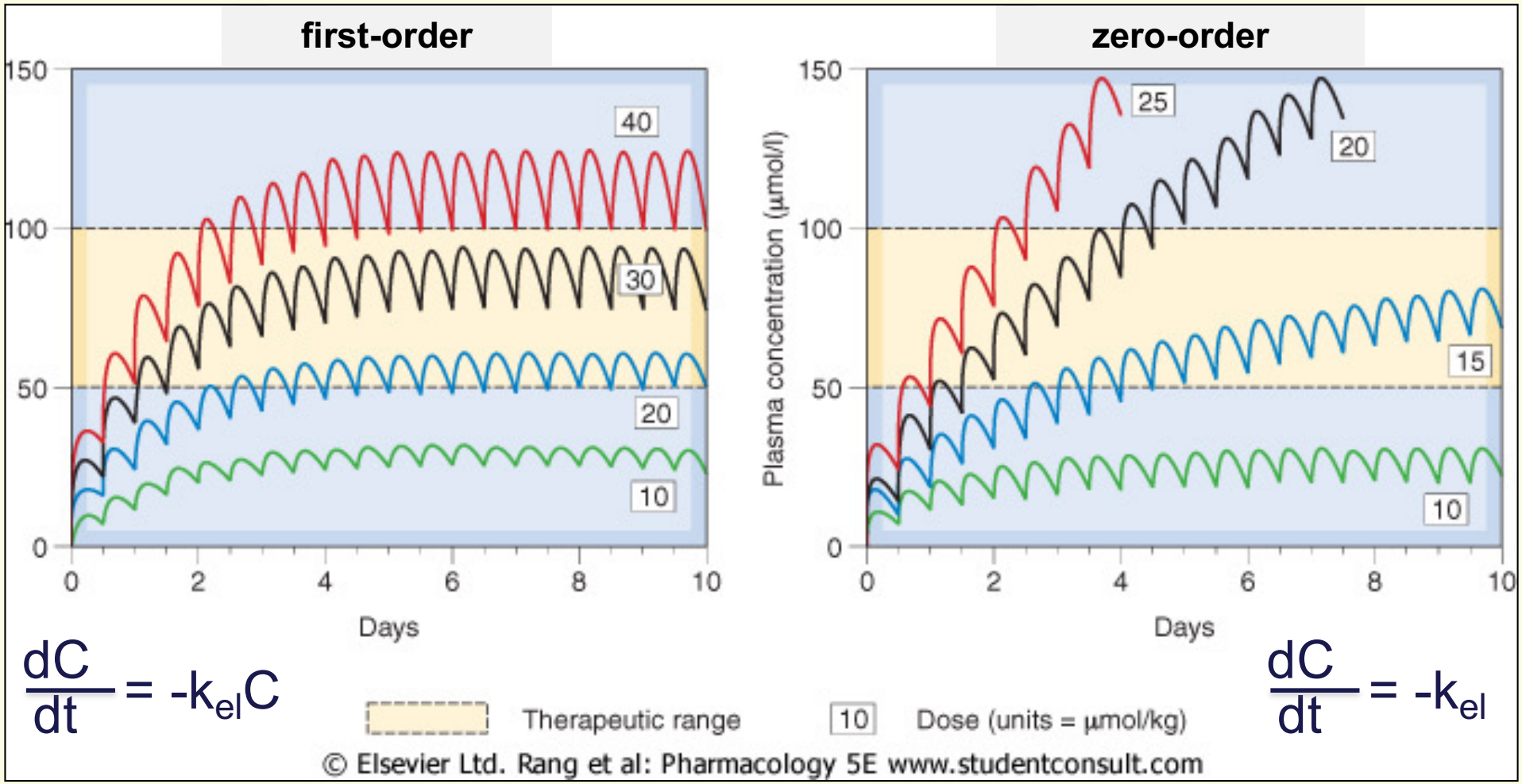
“nonlinear” kinetics

Zero-order at high concentrations (saturation) and first-order at low concentrations.





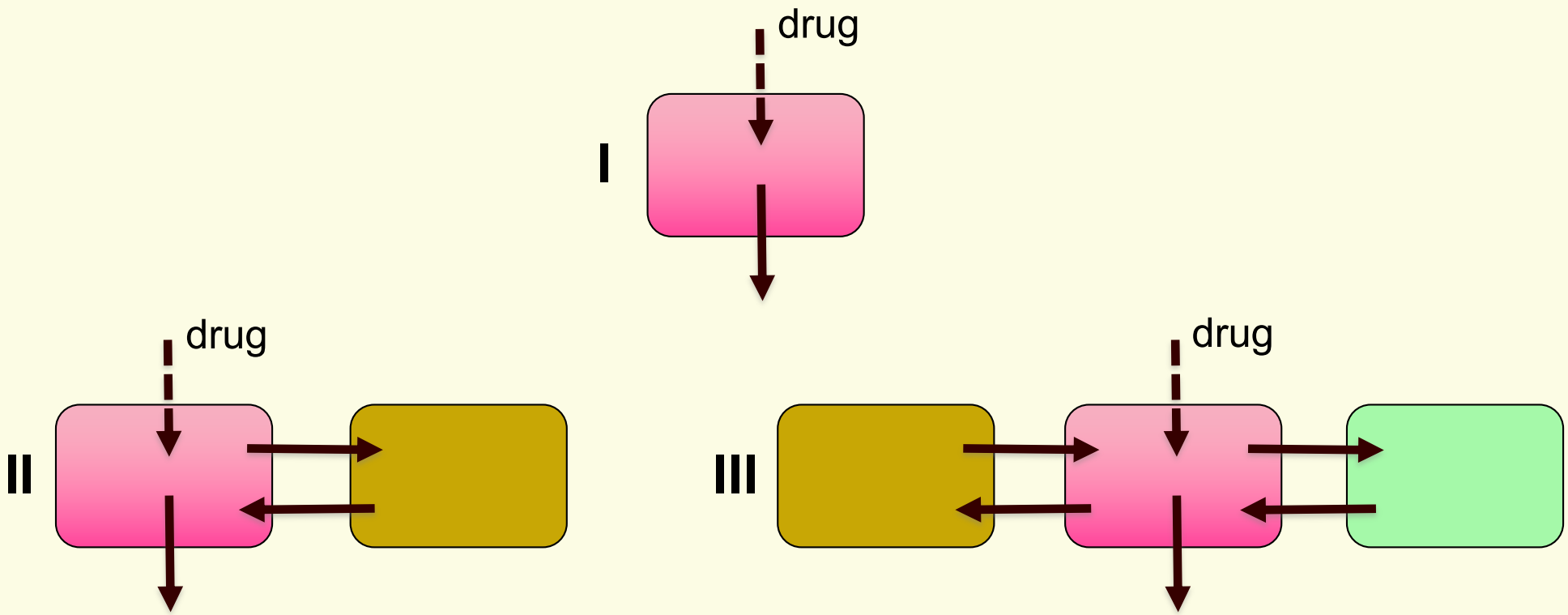
First-order and zero-order kinetics in multiple dosing (example: drugs given orally with 12h interval)



$$\frac{dC}{dt} = -k_{el}C$$

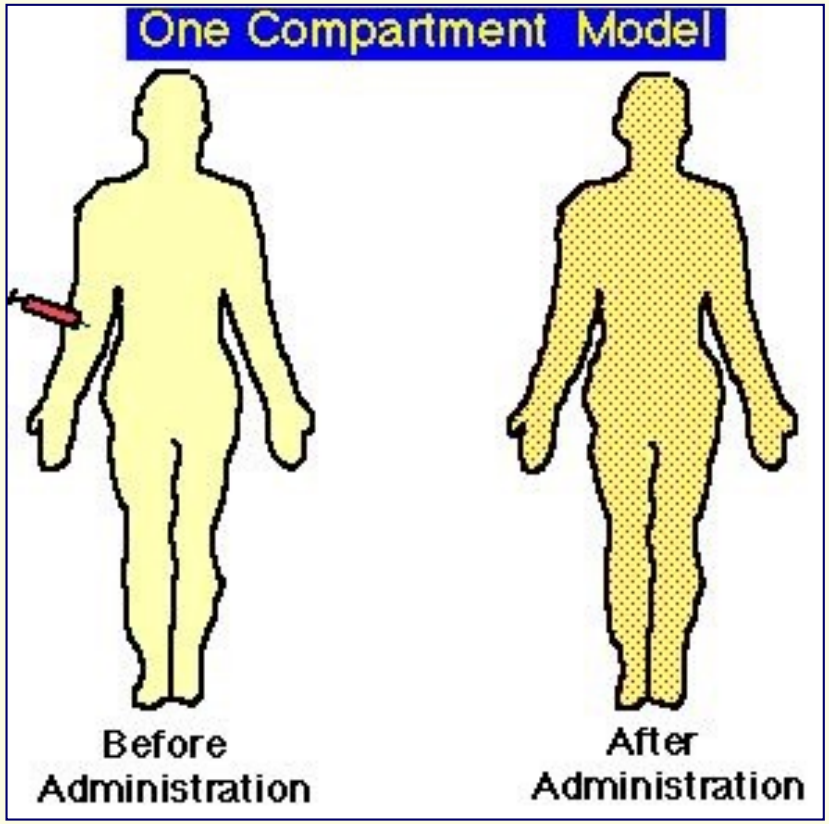
$$\frac{dC}{dt} = -k_{el}$$

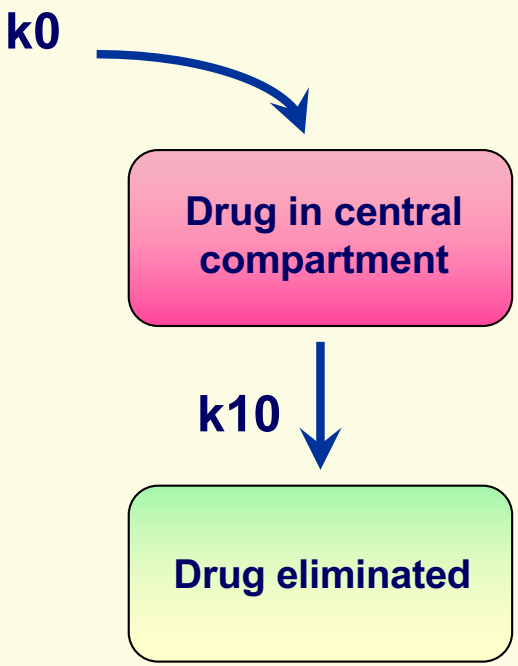
Basic concepts of PK: compartment models



One (I), two (II), and three (III) compartment pharmacokinetic models. In many case the body may even be represented as a single compartment or container for some drugs. For other drugs a two or three compartment model is found to be necessary.

Pharmacokinetics: one compartment model



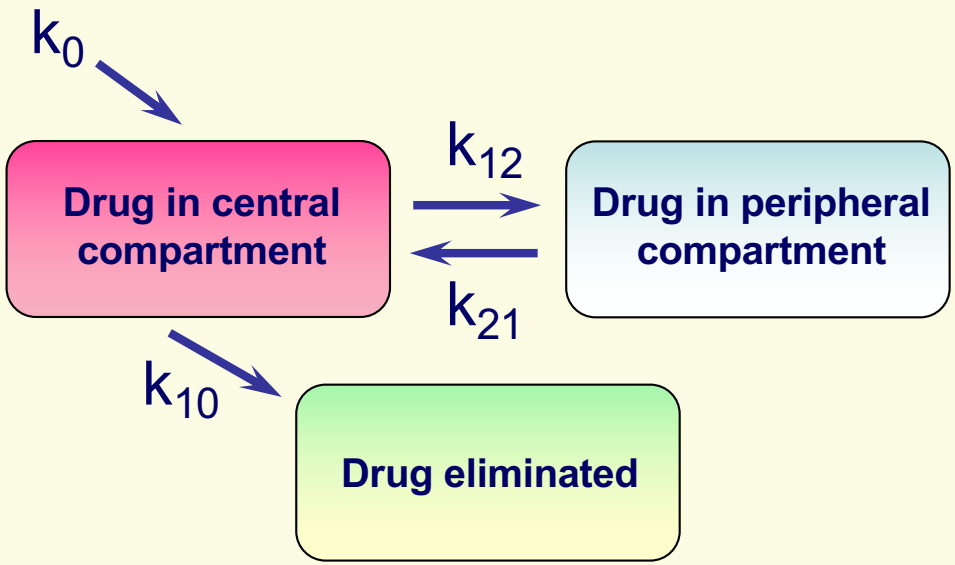


n.b. **central** compartment includes the blood and tissues that have a rapid and profuse blood circulation (liver, kidney,), **peripheral** compartment includes the more slowly perfused tissues

- simplest model

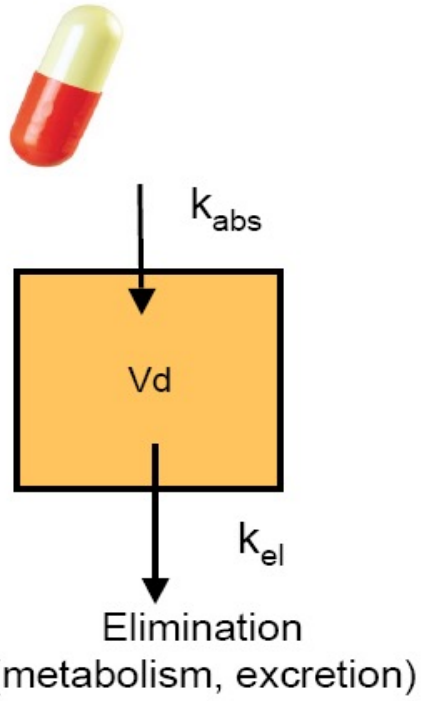
- a diagram of a single compartment model showing the parameters to be measured. The process of excretion can be represented by the rate constant k_{10}. The rate constant k_0 representing an infusion or absorption process.

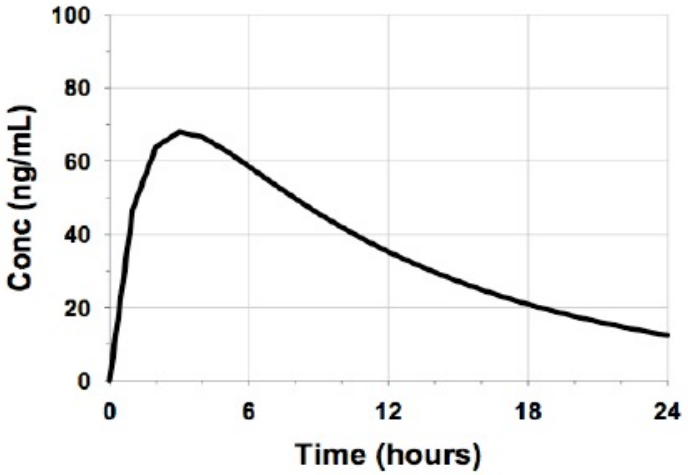
Pharmacokinetics: two compartment model



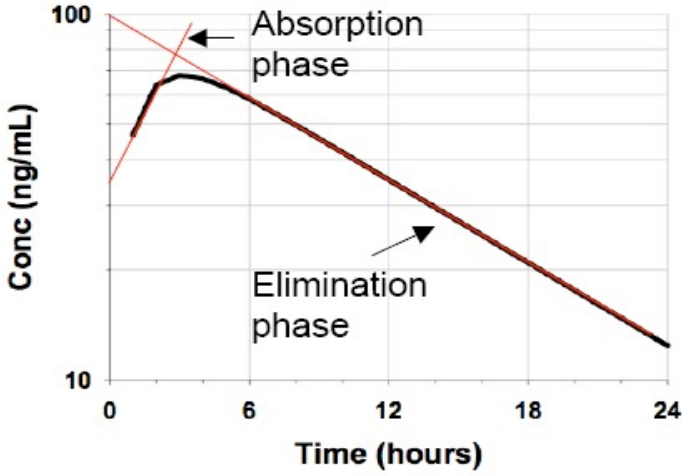
A diagram of a two-compartment model showing the parameters to be measured. The processes of distribution and excretion can be represented by the rate constants k_{12}, k_{21}, and k_{10}. The rate constant k_0 representing an infusion or absorption process. Peripheral compartments – poorly perfused tissues e.g. muscle, fat tissue, etc.).

Oral Dosing - Single Compartment

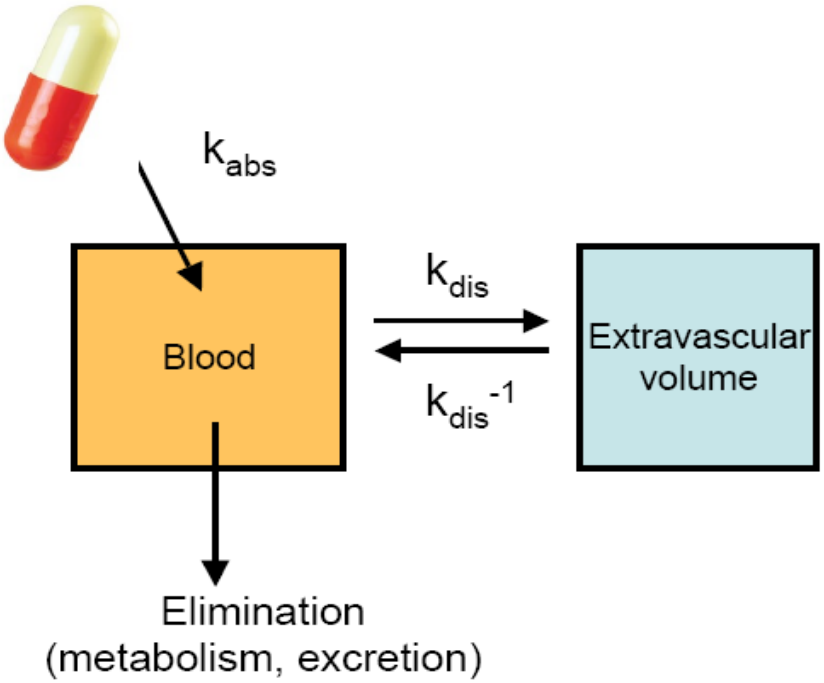


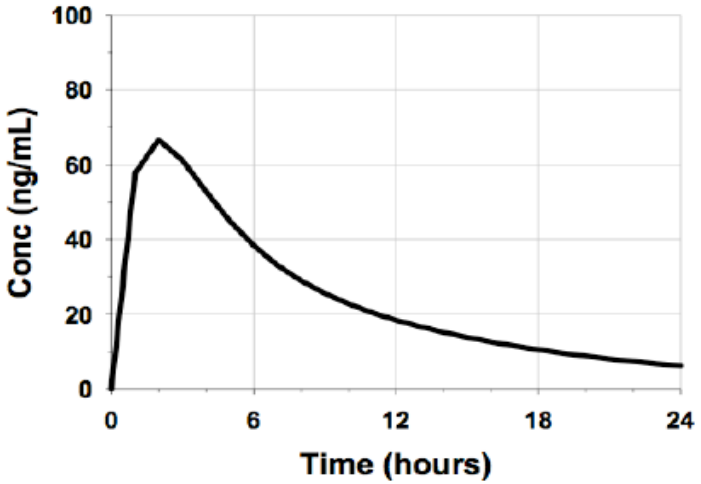


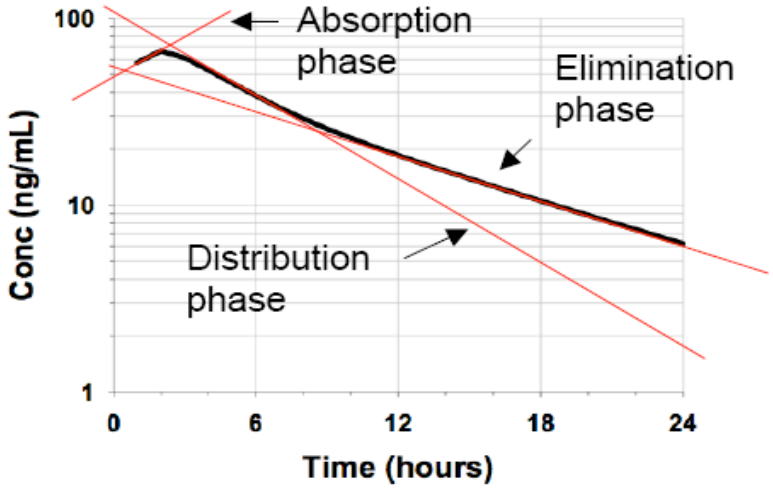
- Takes into account simultaneous absorption, and elimination
- Adequate model for most drugs



Oral Dosing - Two Compartment Model







- Takes into account simultaneous absorption, distribution and elimination processes

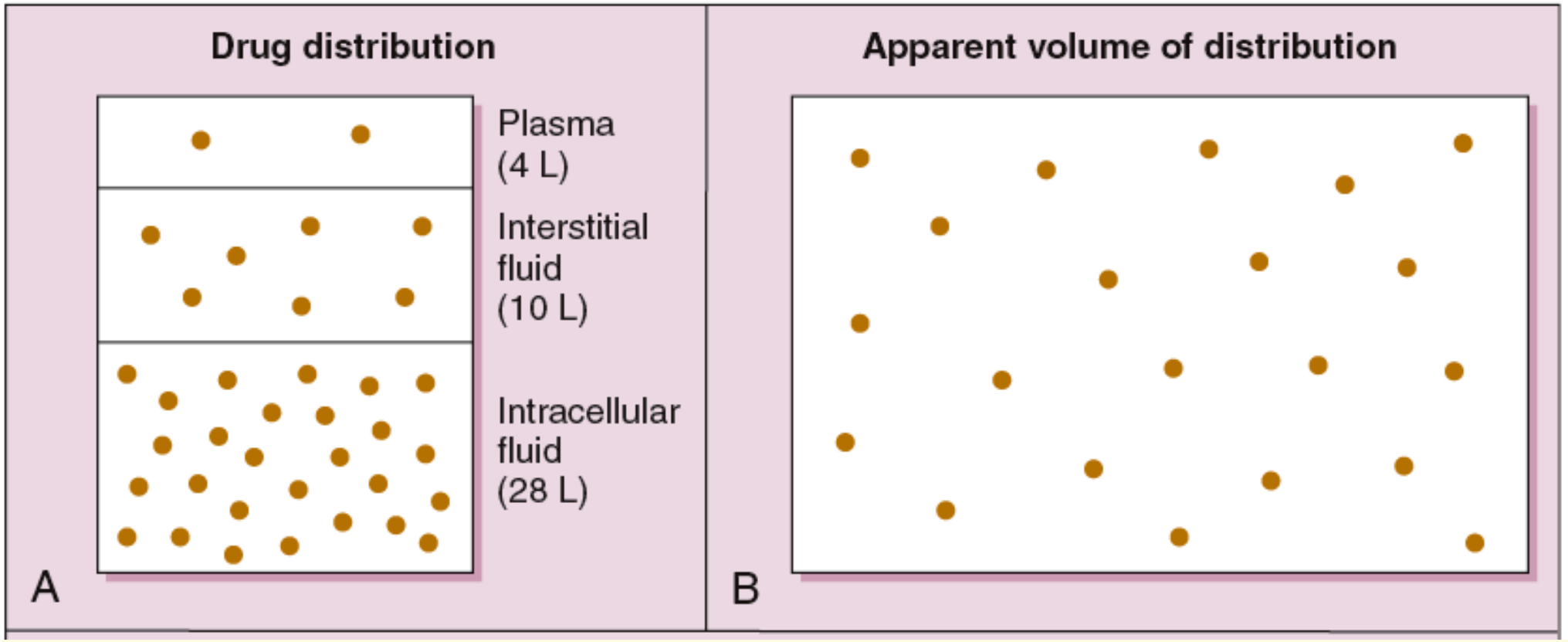
Principal parameters of PK: Apparent Volume of Distribution (Vd)

$$\mathbf{Vd = Q / C_0}$$

Q – dose, C_0- concentration in the central compartment at T(0)

- The apparent volume of fluid in which a drug would need to be dissolved to have the same concentration as it does in plasma.
- The Vd refers to the plasma volume and other physiological fluid spaces and tissues in rapid equilibrium with the plasma (central compartment)
- Vd has no physiological meaning
- The Vd is used to calculate the amount of drug needed to achieve a desired plasma concentration (therapeutic concentration)
- Vd is experimentally determined for each drug.

Principal parameters of PK: Apparent Volume of Distribution (Vd)



$$Q = Vd \times C_0$$

Vd - could be found in the medication monograph for the drug

C_0(or C) - desired plasma concentration (therapeutic concentration)

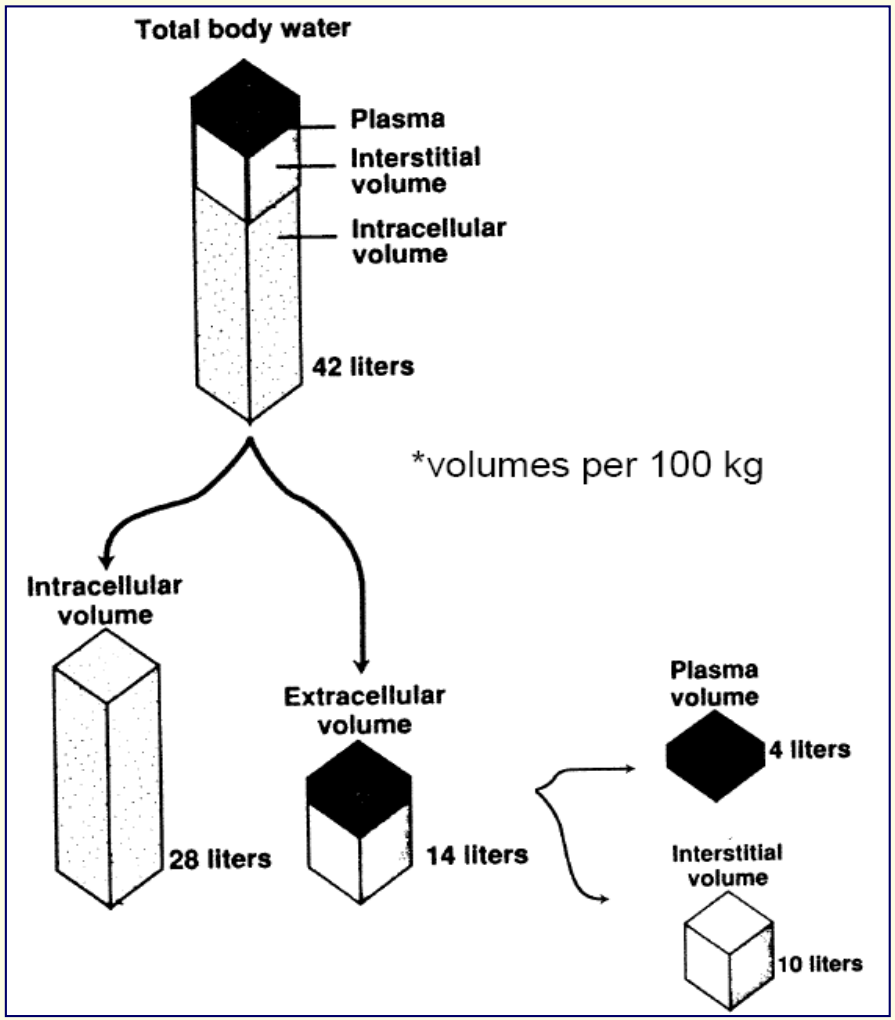
Principal parameters of PK: Apparent Volume of Distribution (Vd)

- For many hydrophilic drugs the Vd is ~ to the extracellular volume
- However, many hydrophobic drugs exhibit Vd far in excess to the extracellular volume.

Example: 500 μg of digoxin in the body of a 70-kg subject results in a plasma concentration of ~ 0.7 ng/ml

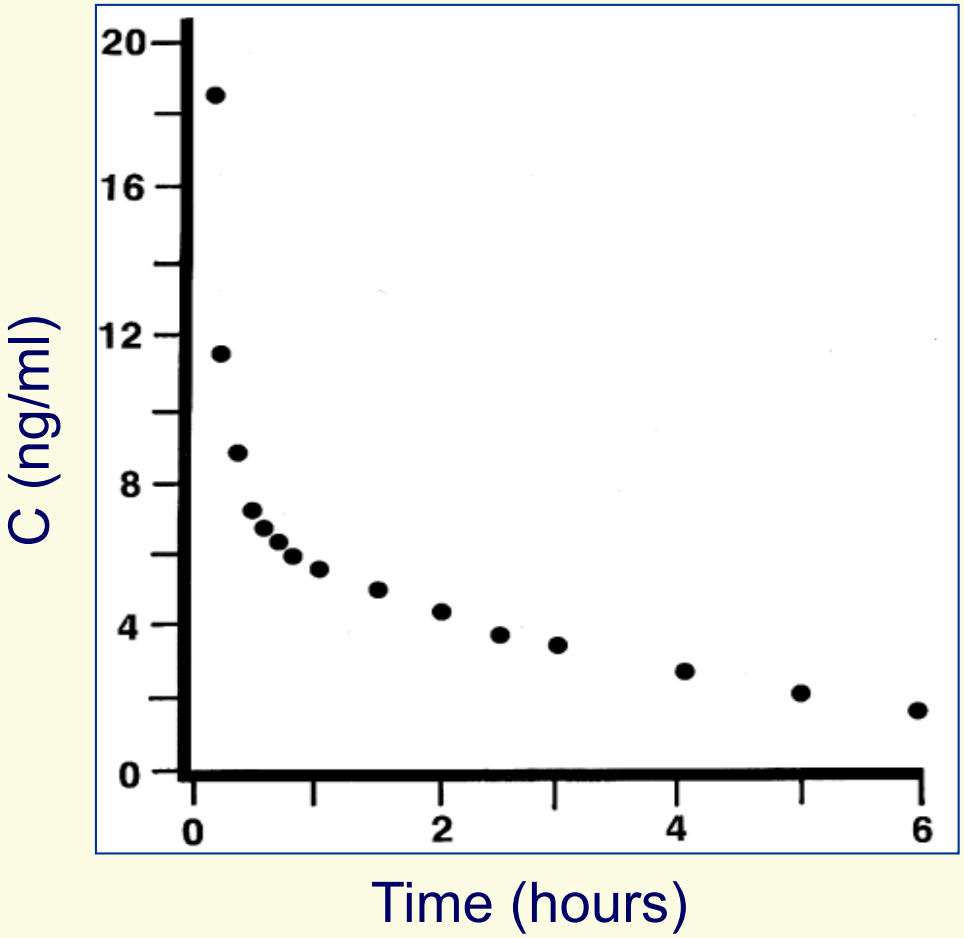
Vd = 700 liters !!

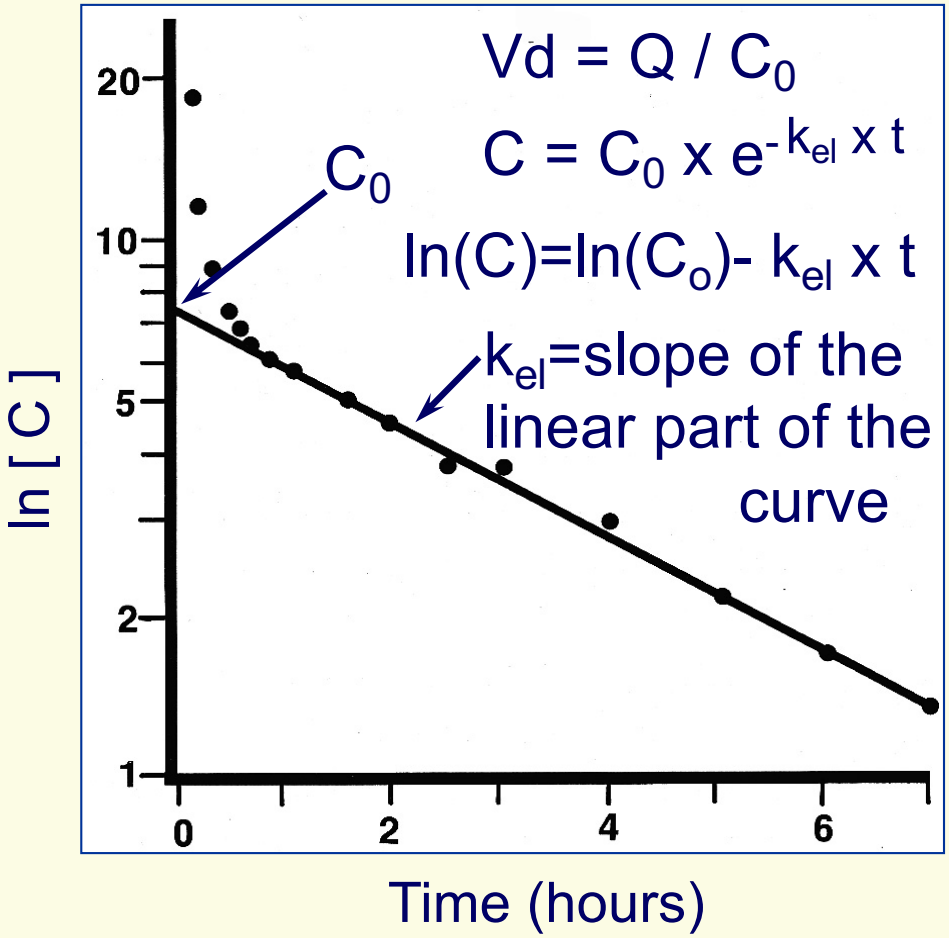
This is due to the preferential distribution of digoxin to muscle and adipose tissue, leaving a very small amount of drug in the plasma.



Experimental assessment of Vd and k_{el}

i.v. injection of dose Q at time 0





C_0 – plasma concentration of drug at T_0 (theoretical)

Principal parameters of pharmacokinetics: elimination rate constant (k_{el}) and half-life ($t_{1/2}$)

- **k_{el}** represents the fraction of drug eliminated per unit of time.
- **$t_{1/2}$** is the time required to eliminate 50% of any amount of drug from the body (after 7 half-lives less than 1% remains).

$$C = C_0 \times e^{-k_{el} \times t} \rightarrow C_0/2 = C_0 \times e^{-k_{el} \times t_{1/2}} \rightarrow \ln C_0/2 = \ln C_0 - k_{el} \times t_{1/2}$$

$$\rightarrow k_{el} \times t_{1/2} = \ln C_0 - \ln C_0/2 \rightarrow k_{el} \times t_{1/2} = \ln 2 \rightarrow t_{1/2} = \ln(2) / k_{el}$$

$$\boxed{t_{1/2} = 0.693 / k_{el}}$$

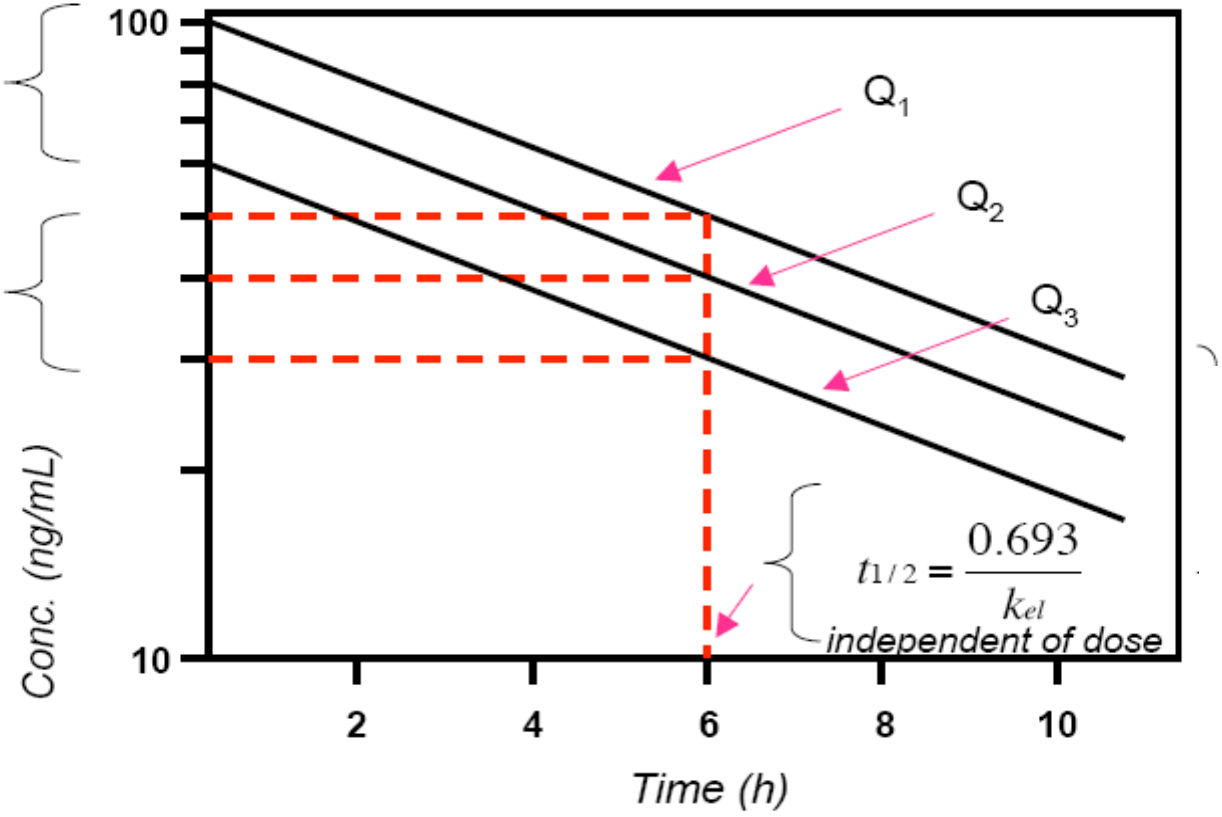
$t_{1/2}$ and k_{el} are independent of dose (Q)

$$Co = \frac{Q}{Vd}$$

varies with dose

$$\frac{Co}{2} = Co \cdot e^{-kel \cdot t}$$

varies with dose



For the majority of drugs:

- elimination is a first-order process
- C_0 varies with dose
- k_{el} and therefore, $t_{1/2}$ is independent of dose (Q)

Principal parameters of pharmacokinetics: Clearance (Cl)

- **Cl** is the volume/part of Vd which is completely cleared of drug per unit of time.
- **Cl** is one of the most fundamental PK parameters that is used to evaluate efficiency of drug removal from the body

$$Cl = k_{el} \times Vd \qquad Cl = 0.693\ Vd / t_{1/2}$$

$$t_{1/2} = 0.693\ Vd / Cl$$

- **Cl** can be calculated either as TOTAL **Cl**, or **Cl**/organ

$$\mathbf{Cl_T = Cl_{KIDNEY} + Cl_{LUNG} + Cl_{other\ organs}}$$

$$\mathbf{e.g.\ Cl_{KIDNEY} = \frac{V_u \times U_x}{t \times P_x}}$$

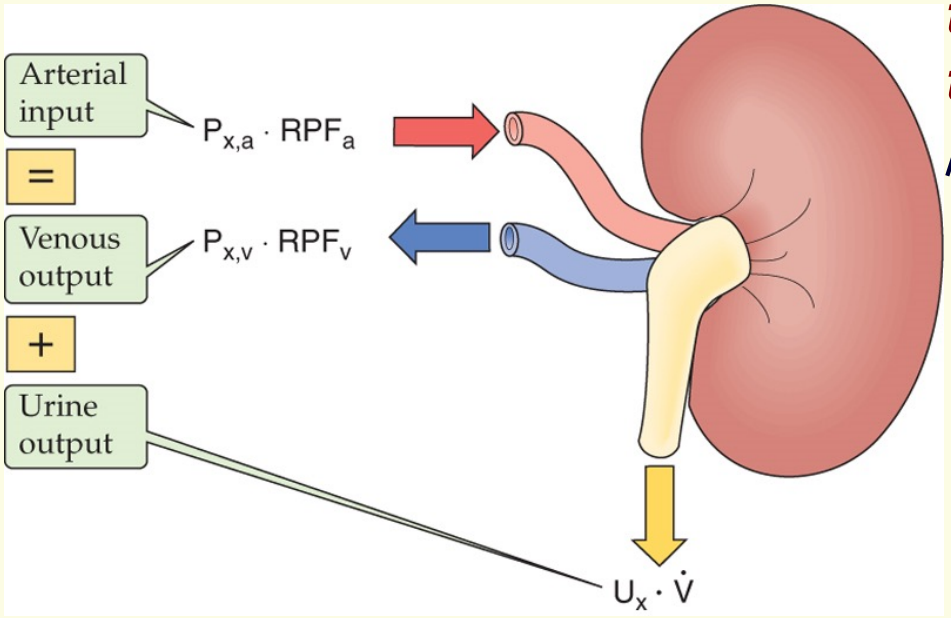
Renal Clearance

- reflects the renal excretion ability for the given substance (both glomerular and tubular functions)

- for substances that are neither reabsorbed nor secreted it reflects the glomerular function – the Glomerular Filtration Rate (GFR).

- for substances that are totally cleared by the kidney in a single passage it reflects the Renal Plasma Flow (RPF).

Clearance



Solute mass balance: For any solute (X) that is not degraded or accumulated in the kidney:

$$\overbrace{\underbrace{P_{X,a}}_{\frac{mmole}{mL}} \cdot \underbrace{RPF_a}_{\frac{mL}{min}}}^{\text{Arterial input of X}} = \overbrace{\left(\underbrace{P_{X,v}}_{\frac{mmole}{mL}} \cdot \underbrace{RPF_v}_{\frac{mL}{min}}\right)}^{\text{Venous output of X}} + \overbrace{\left(\underbrace{U_X}_{\frac{mmole}{mL}} \cdot \underbrace{\dot{V}}_{\frac{mL}{min}}\right)}^{\text{Urine output of X}}$$

Clearance definition:

$$\overbrace{P_{X,a} \cdot C_X}^{\text{Virtual arterial input}} = \overbrace{\vec{0}}^{\text{Virtual venous output}} + \overbrace{(U_X \cdot \dot{V})}^{\text{Actual urine output}}$$

$$C_X = \frac{U_X \cdot \dot{V}}{P_X}$$

C_x – clearance of substance X

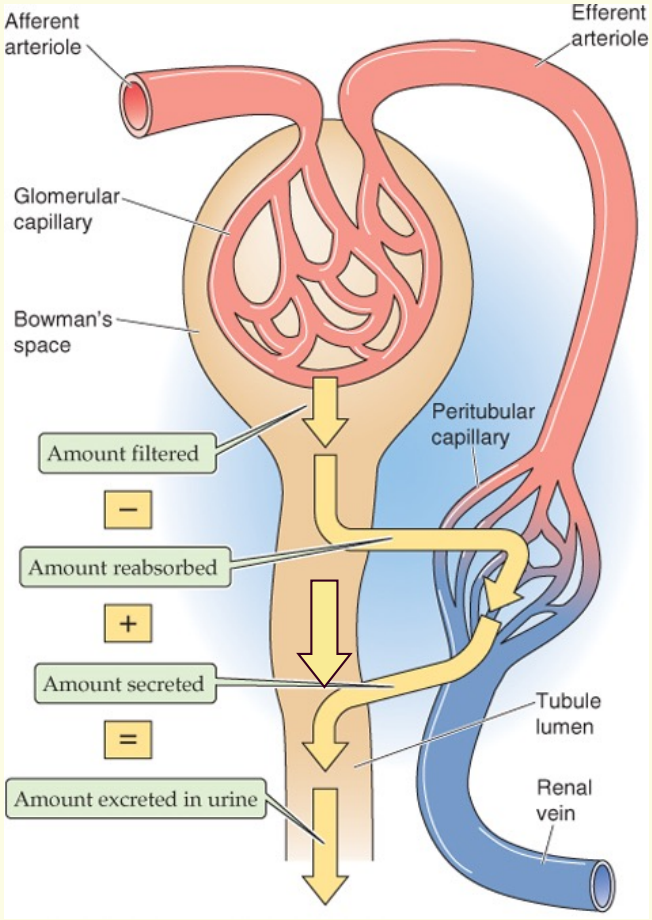
U_x – concentration of X in the urine

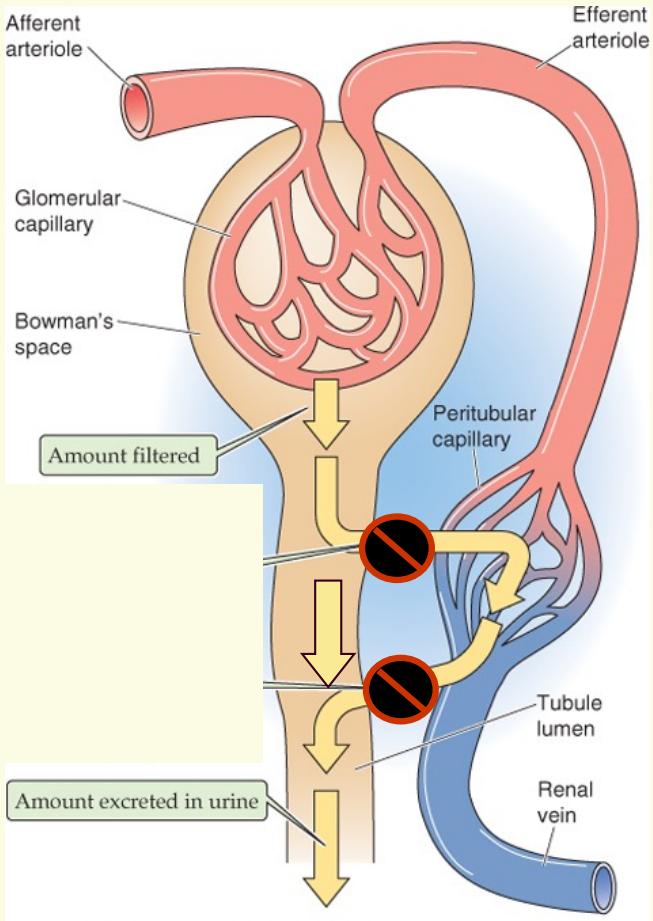
P_x – concentration of X in the plasma

$\dot{V}$ – urine flow (ml/min)

RPF – renal plasma flow

Clearance of substances (drugs) that are neither reabsorbed nor secreted by the renal tubule





Input into glomerulus Output into urine

$$P_{x,a} \cdot GFR = U_x \cdot \dot{V}$$

$$GFR = \frac{U_x \cdot \dot{V}}{P_x}$$

GFR = Clearance!

in humans GFR = 120 ml/min

Clearance of substances (drugs) that are completely cleared by the kidney in a single passage

Example:

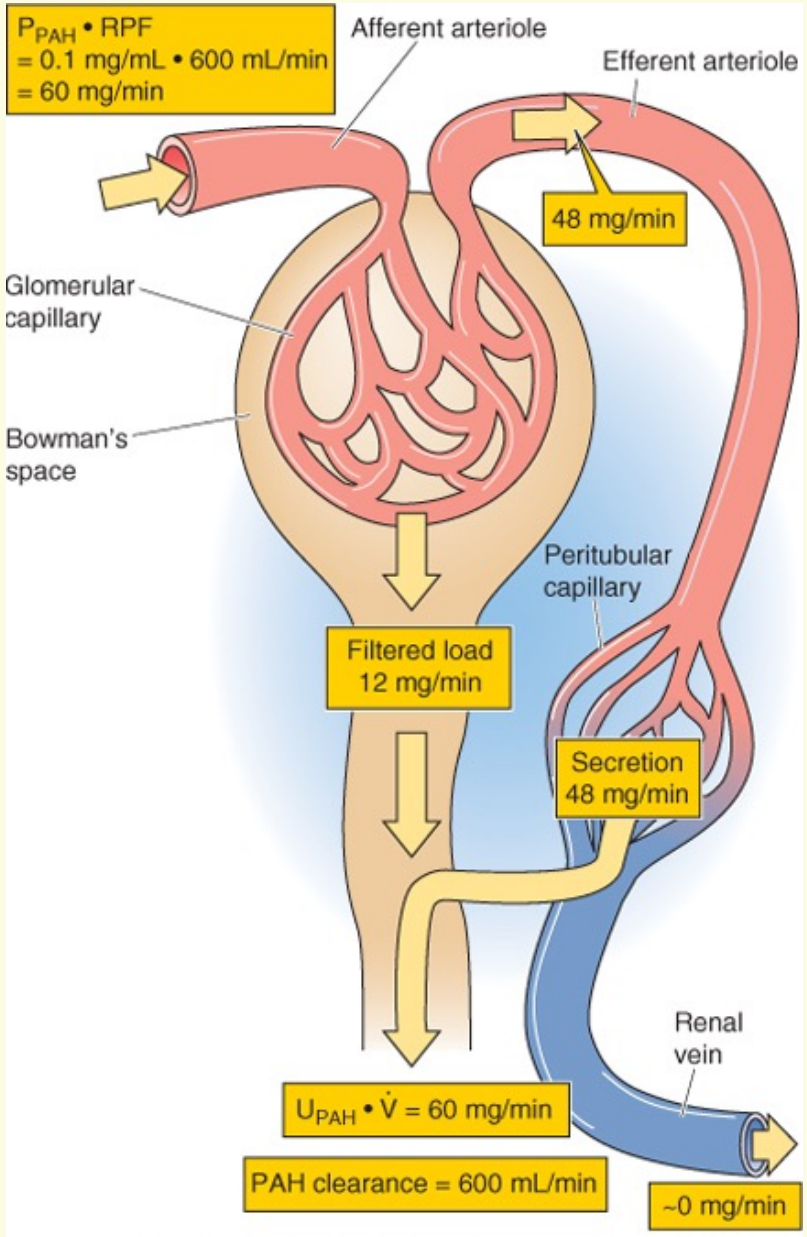
p-Aminohippuric acid (PAH)

$$\underbrace{P_{X,a}}_{\frac{mmole}{mL}} \cdot \underbrace{RPF_a}_{\frac{mL}{min}} = \left(\underbrace{P_{X,v}}_{\frac{mmole}{mL}} \cdot \underbrace{RPF_v}_{\frac{mL}{min}} \right) + \left(\underbrace{U_X}_{\frac{mmole}{mL}} \cdot \underbrace{\dot{V}}_{\frac{mL}{min}} \right)$$

Arterial input of X | Venous output of X | Urine output of X

$$C_{PAH} = RPF = \frac{U_{PAH} \cdot \dot{V}}{P_{PAH}}$$

- Clearance of PAH is used as index of RPF (~600 ml/min)



Clearance (C_X) may vary between 0 and the RPF value

Cx = RPF

If a substance is totally removed from blood in a single pass…

$$P_{X,a} \cdot RPF_a = P_{X,v} \cdot RPF_v + U_x \cdot \dot{V}$$

$$RPF_a = \frac{U_X \cdot \dot{V}}{P_{X,a}} = C_X$$

e.g., p-aminohippurate (PAH)

Cx = 0

If a substance does not appear in the urine…

$$U_X = 0$$

$$C_X = 0$$

e.g., glucose

Clearance Examples

Solute (X)	Normal clearance values (ml/min)	Solute properties
Glucose	0	Freely filtered, and completely reabsorbed
Inulin	120 (equal to GFR)	Freely filtered, not reabsorbed, and not secreted
PAH	600 (equal to RPF)	Freely filtered, not reabsorbed, and completely secreted
If drugs A and B are known to be freely filtered		
Drug (A)	40	Partially reabsorbed
Drug (B)	400	Secreted, and secretion > reabsorption

Exercise 1: Single Compartment Model Equations

Your patient is suffering from a severe infection with gram-negative bacteria that requires i.v. infusion of the antibiotic cefpirome. Pharmacokinetics properties of this drug are the following (from the drug prescription monograph):

- Cl = 0.1 L / min

- Vd = 25 L

- therapeutic concentration = 0.5 μg / mL

Question 1: what is the half-life for cefpirome?

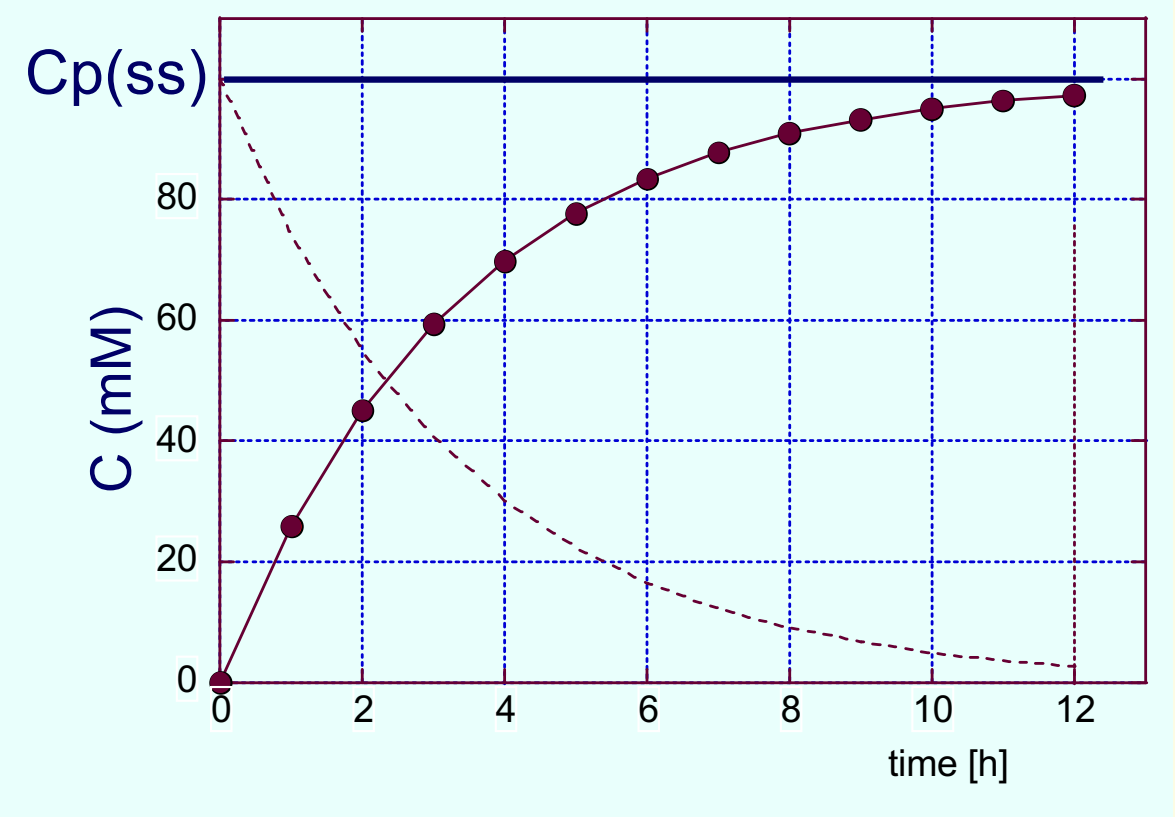
Exercise 2: Single Compartment Model Equations

What dose of cefpirome should receive your patient (IV bolus) to achieve the therapeutic concentration?

Exercise 3: Single Compartment Model Equations

your patient received an initial dose of 10 mg. What will be the plasma concentration of the drug after 4 hours?

Continuous drug administration and steady state drug concentration Cp(ss) (therapeutic concentration)

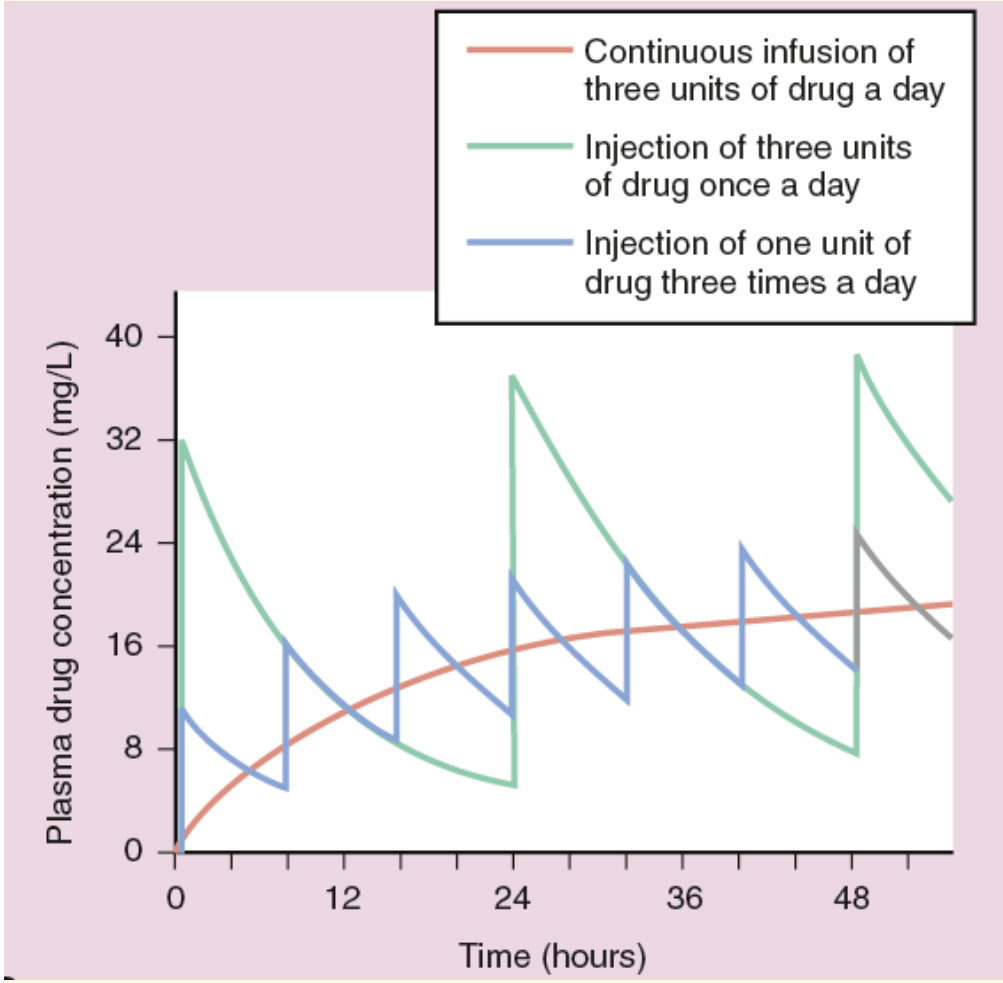


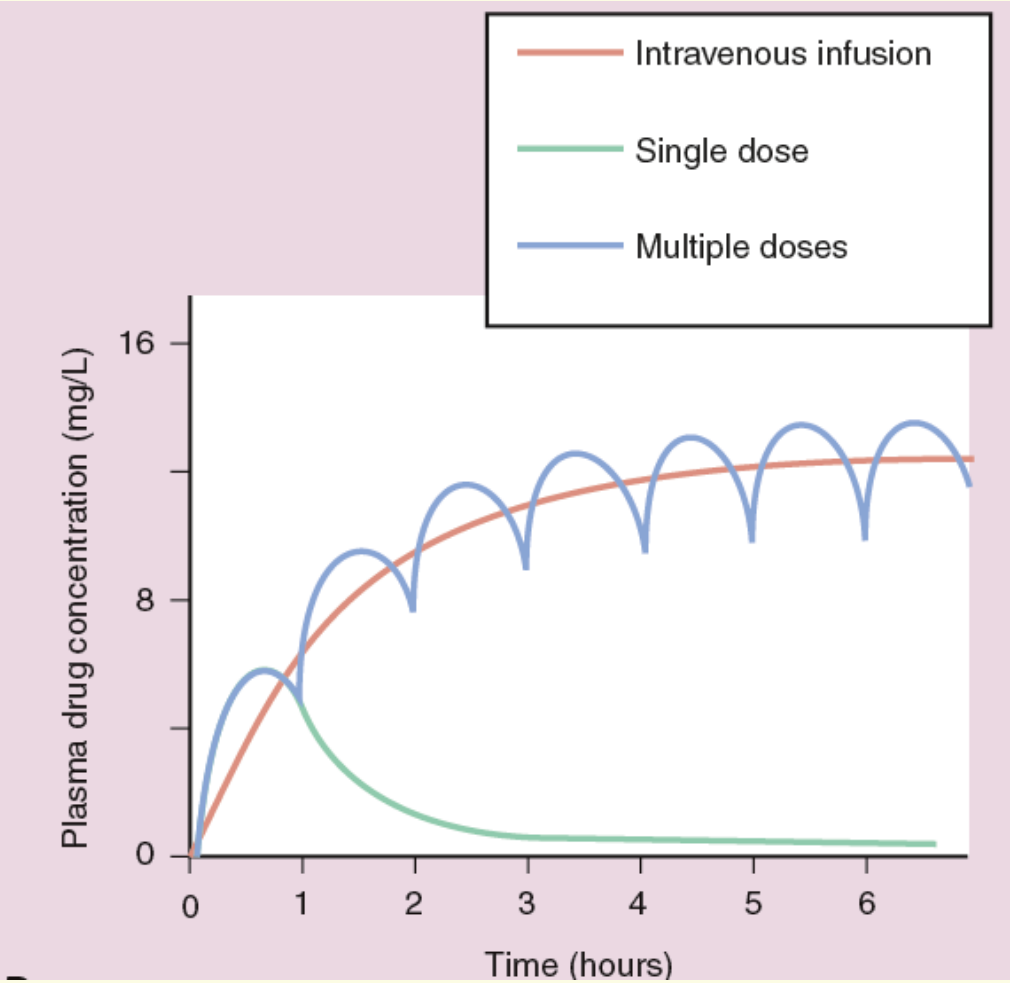
The steady state is reached when:

rate of administration (Qr) = rate of elimination

or, rate of administration Qr = Cp(ss) x Cl

Multiple dosing and steady state

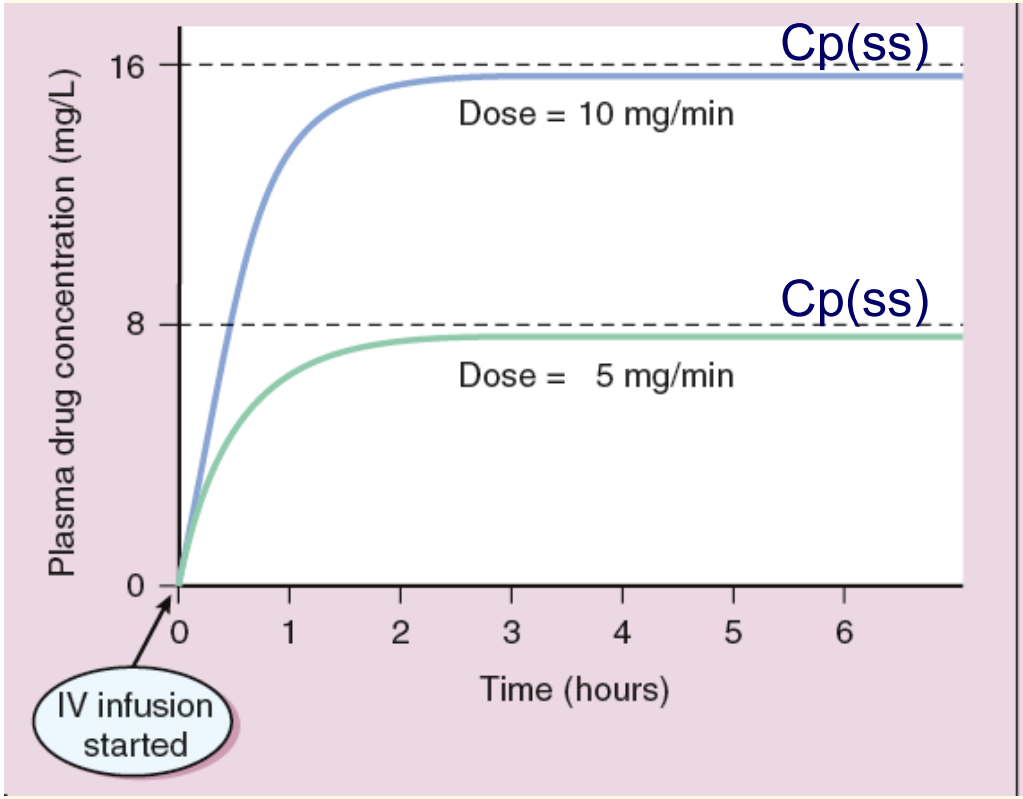


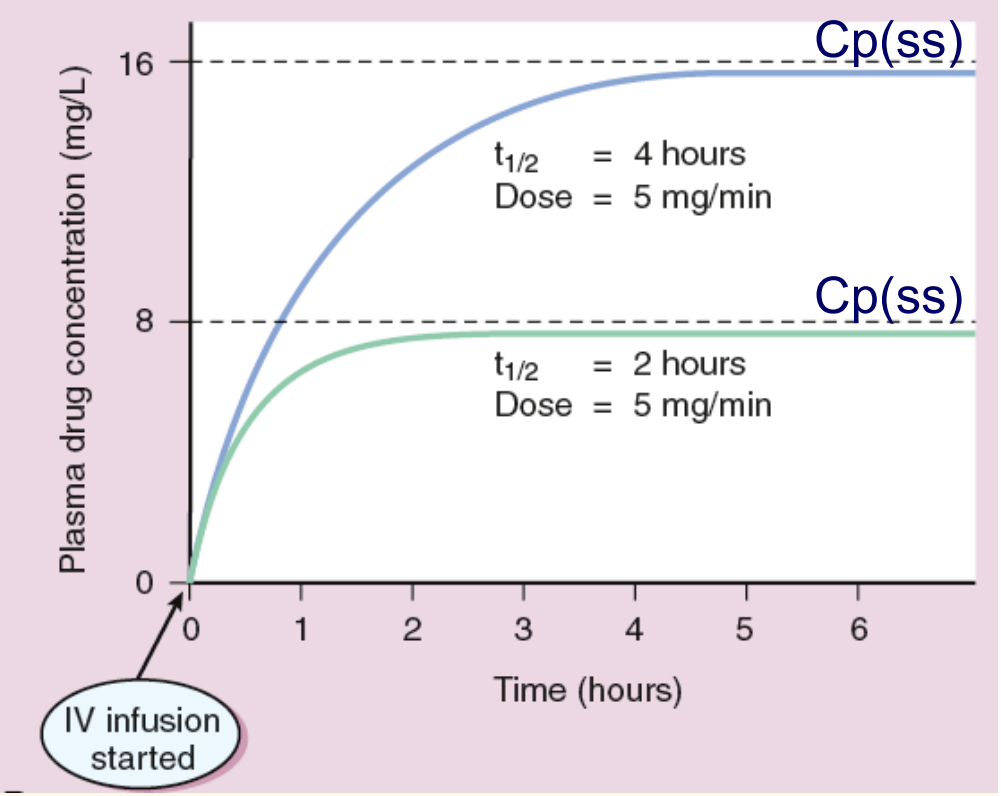


i.v. drug delivery

oral drug delivery

Continuous drug administration and steady state drug concentration Cp(ss)





The Cp(ss) is proportional to the dose administrated per unit of time

$Cp(ss)=Qr/Cl$

The Cp(ss) is directly proportional to $t_{1/2}$ and inversely to Vd

$Cl=0.693_x Vd/t_{1/2}$

$Cp(ss)=Qr_x t_{1/2}/0.693_x Vd$

Maintenance Dosage Calculations

At Steady State:

Rate of administration = Rate of elimination

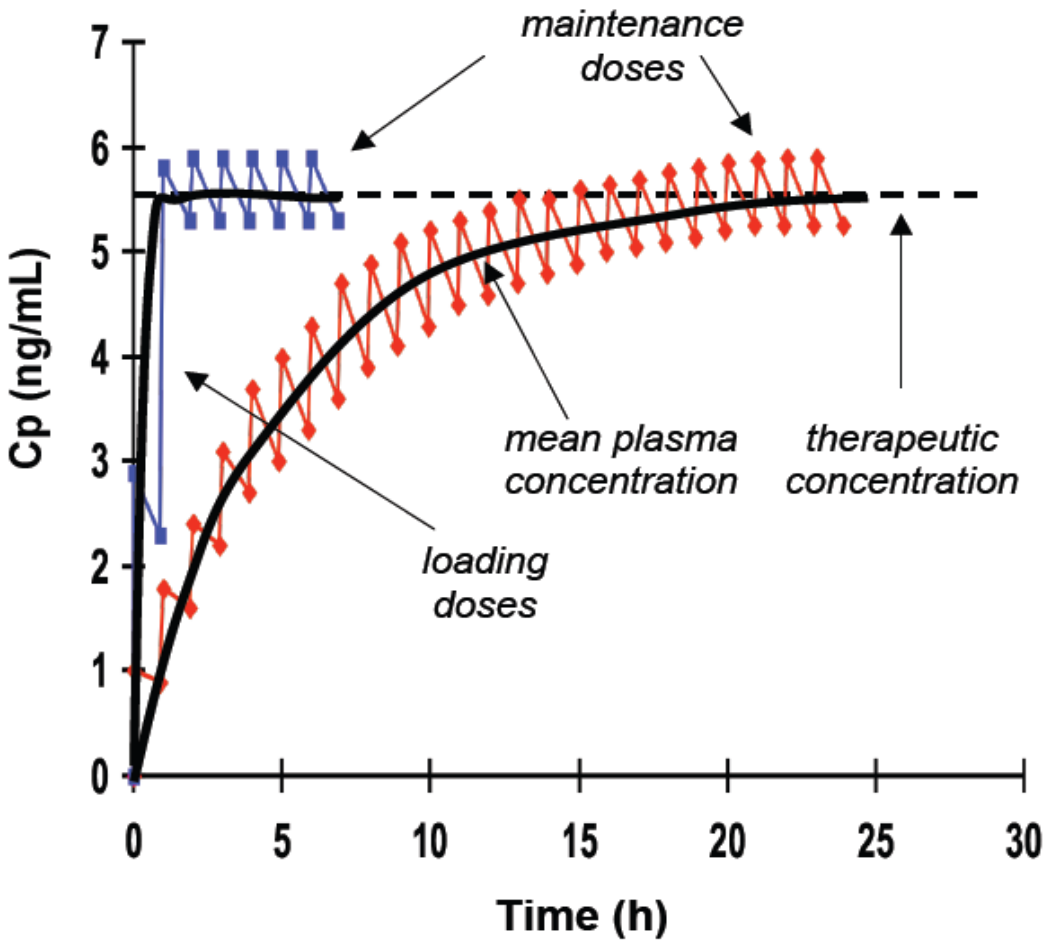
$$Qr = Cp(ss) \cdot Cl$$

$$\frac{Qm}{Tm} = Cp(ss) \cdot Cl$$

Therefore, to maintain a particular steady state plasma concentration (Cp(ss)), a maintenance dose of Qm must be given at intervals of Tm:

$$Qm = Cp(ss) \cdot Cl \cdot Tm$$

Multiple dosing and steady state - Loading dose



- **Rule of Thumb for the Majority of Drugs**: With continuous IV infusion or repeated maintenance doses, Cp(ss) is effectively reached after approximately 3 half-lives (3 x $t_{1/2}$)

- For drugs with a long $t_{1/2}$, attainment of Cp(ss) and therefore, therapeutic concentrations maybe unacceptably long
- In this case, a loading dose QI can be used to achieve Cp(ss) more rapidly

$$Cp(ss) = \frac{QI}{Vd}$$

$$QI = Cp(ss) \cdot Vd$$

Exercise 4: Single Compartment Model Equations

your patient suffers from hypertension that can be treated effectively by losartan. In the product prescription monograph you can obtain the following information about the drug:

- Cl = 600 mL/ min
- Vd = 34 L
- Therapeutic concentration = 100 ng / mL

1) Initially, a continuous IV infusion is chosen to treat the patient. What is the rate of infusion that should be used?

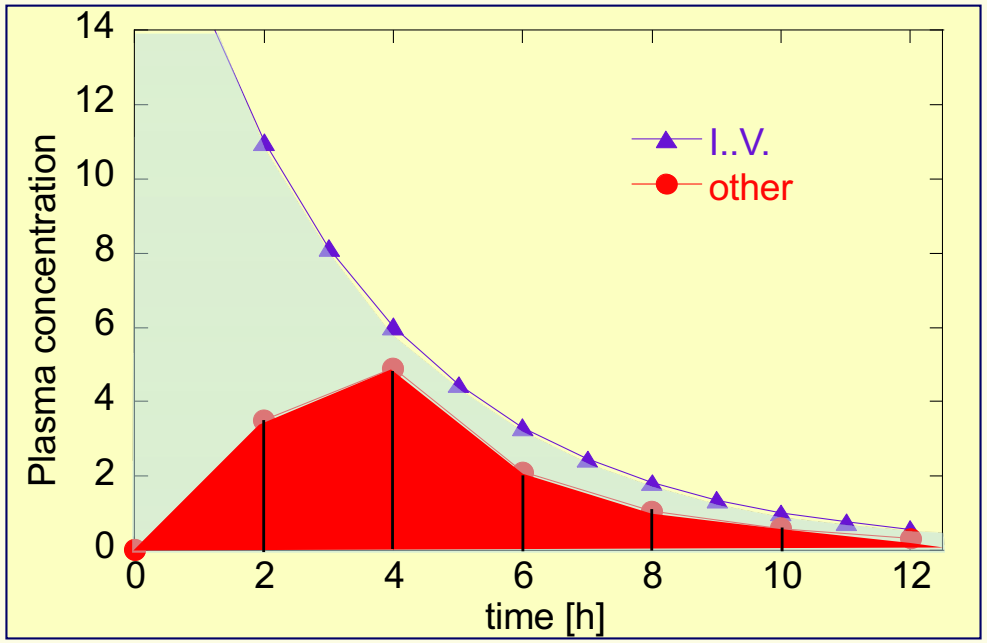
Exercise 5: Single Compartment Model Equations

If a more rapid onset of action is desired, what loading dose could be given as single IV injection?

Exercise 6: Single Compartment Model Equations

Following the loading dose, what is the dosing interval required to maintain therapeutic concentration with an IV maintenance dose of 43.2 mg ?

Pharmacokinetics: Bioavailability



$$\text{Bioavailability (F)} = \frac{\text{AUC}}{\text{AUC i.v.}}$$

AUC – area under the curve

- A relative term that compares the total amount of parent drug that is delivered to the central compartment by oral, mucosal, parental, inhalation or percutaneous routes vs. i.v. route.
- For i.v. the bioavailability is = 1 (100% bioavailable)
- For other routes, the bioavailability is < 1 due to:
  - Incomplete absorption
  - first-pass metabolism
- Determined by comparison of AUC for a single i.v. dose and other ways of dosage.

Exercise 7: Single Compartment Model Equations

What is the dosing interval required to maintain the therapeutic concentration of losartan (F_{oral} = 0.32) with an oral maintenance dose of 43.2 mg ?