Semester I.
Seminar 6.

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Exam titles 11-12

11.

- The clearance
- Selective α-adrenoceptor blockers
- Pharmacology of the liver and the gall bladder

12.

- Plasma concentrations after repeated administration, loading dose and maintenance dose
- Metabolism of chatecholamines and pharmacological modulation
- Pharmacological treatment of bronchial asthma

The renal clearance

- Def.: Volume of plasma cleared of drug per unit time by the kidneys
- creatinine rather than urea clearance has become the routine clinical measure of renal functional status because it more closely reflects the glomerular filtration rate.

$$CL_r = \frac{C_u \times V_u}{C_p}$$

C_u = urinary concentration
V_u = rate of flow of urine
(in units of volume/time (e.g. ml/min or ml/min/kg))
C_p = plasma concentration
(units of concentrations cancel out)

- *CL*r varies greatly for different drugs:
  - from less than 1 ml/min to 700ml/min

theoretical maximum set by the renal plasma flow

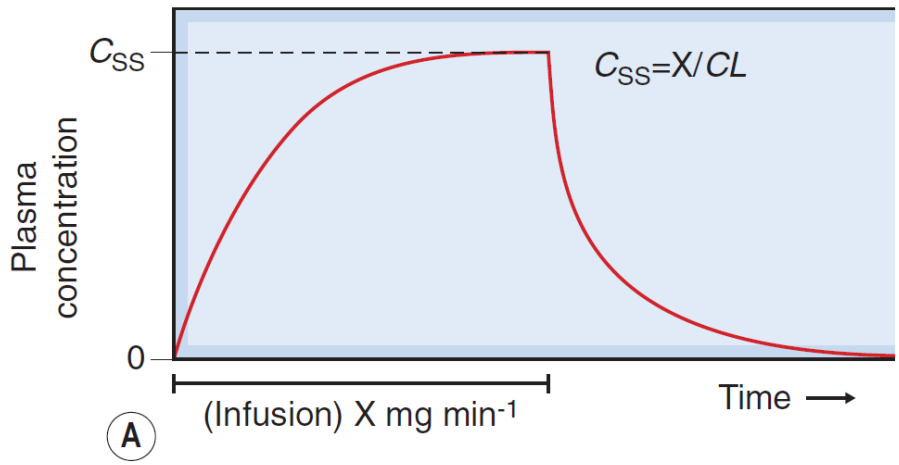
The Total Clearance

- Def.: Volume of plasma cleared of drug per unit time by all routes.
- $Cl_{tot} = CL_r + CL_{met} + CL_{breath} + CL_{faeces} + CL_{...}$ etc.
- The total clearance can be calculated.
  The concentration of the drug should get to a *steady state*
  - *Steady state*= the rate of input to the body is equal to the rate of elimination
  - a constant-rate intravenous infusion (delivering, say, X mg of drug per h) should be used (= dose-rate)
  - The steady state plasma concentration (C_{ss}) should be measured

$$X = C_{ss} \times Cl_{tot}$$

$$\downarrow$$

$$CL_{tot} = \frac{X}{C_{ss}}$$



The Total Clearance

- Def.: Volume of plasma cleared of drug per unit time by all routes.

- Another calculational route arises from the definiton:
- $CL_{tot} = k_{el} V$ (or $CL_{tot} = k_{el} V_d$)
- K_{el} = elimination constant (unit: min^{-1})
  - k = Fraction of drug in the body removed per unit time
- V = volume (ml) (or V_d = volume of distribution (ml))

The connection between the two formulas

- The rate of any process can be described as the kQ, where k is a constant and Q is the drug amount
- Rate of elimination = k_{el} Q,
- Remembering that **V_d= Q/c_p (last seminar)➔**
  - And therefore Q= c_p V_d
  - Rate of elimination = k_{el} c_p V_d
- Rate of elimination for whole body (X) = **X = CL_{Total} c_p**

Combining the two,

CL_{Total} c_p = k_{el} c_p V_d and simplifying gives:

CL_{Total} = k_{el} V_d

Plasma concentrations after repeated administration,
loading dose and maintenance dose

The loading dose

- If we don't want to wait 4-5 half-lifes' time for the drug to achieve steady state concentration, a loading dose ("saturating dose" in hungarian) is needed
- Can be calculated by using the equation from last seminar:

$$V_D = \frac{Q}{C_P} \quad \rightarrow \quad Q = V_D * C_P$$

V_D = volume of distribution
C_P = plasmal concentration
Q = dose (loading dose)

- With a difference: instead of C_p we use C_{ss}
  This comes from the definition of loading dose:
  to achieve steady state concentration in the total volume of distribution:

$$Q = V_D * c_{SS}$$

If the bioavailability (see on a later seminar) of the drug is less than 100%, than we use a factor: $Q = \frac{V_D * C_{SS}}{F}$

example: bioavailability is 70% ➔ F=0.7

The maintenance dose

- If we administer drugs continuosly, we should use a dose-rate (mg/h), that holds drug concentration in the therapeutic window
- This can be calculated using an equation from this seminar:

$$X = C_{SS} \times Cl_{tot}$$

- Again, if the bioavailability of the drug is not 100%, then a factor should be used: $X = \frac{C_{SS} \times Cl_{tot}}{F}$

Blood level curves of drugs after single administration

- One compartment model, *intra venous* administration
- One compartment model, *per os* administration
- Two compartment model, *intra venous* administration

Blood level curves of drugs after continuous administration

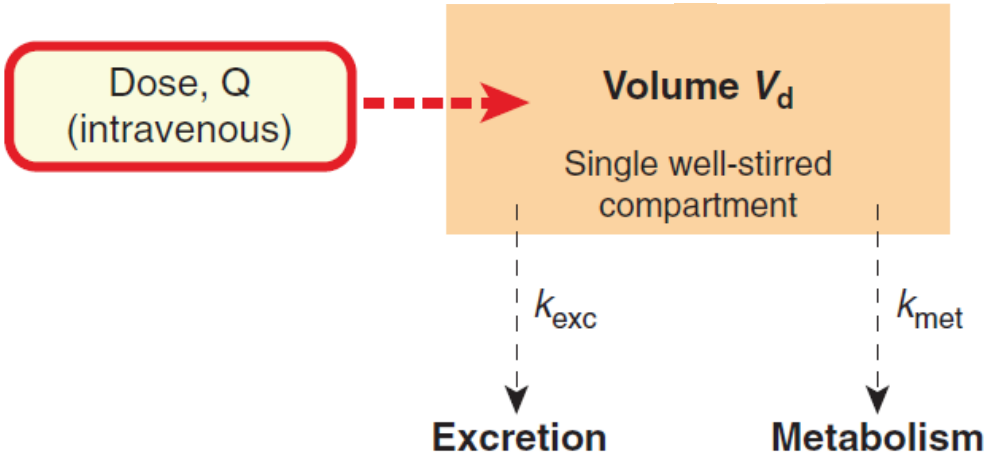
- One compartment model, *intra venous* administration
- One compartment model, *per os* administration

First-order kinetics

Zero-order/Saturation kinetics vs First-order kinetics

- One compartment model, *intra venous* administration

One-compartment model, single bolus *intra venous* administration



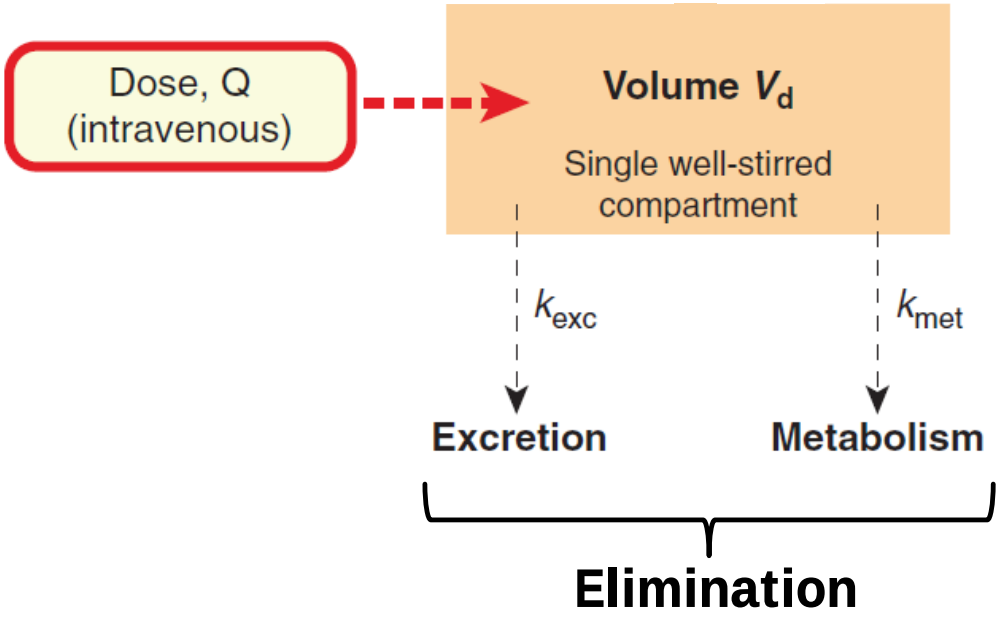
Consider a highly simplified model of a human being, which consists of a single well-stirred compartment, of volume *V*d (distribution volume), into which a quantity of drug Q is introduced rapidly by intravenous injection, and from which it can escape either by being metabolised or by being excreted.

$$Q = \underbrace{c_0 \; x \; V_d}$$

The quantity of drug
in the body
when it is administered (at t_0 time)

The quantity of drug in the body when it is administered as a single bolus is equal to the administered dose Q.

One-compartment model, single bolus *intra venous* administration



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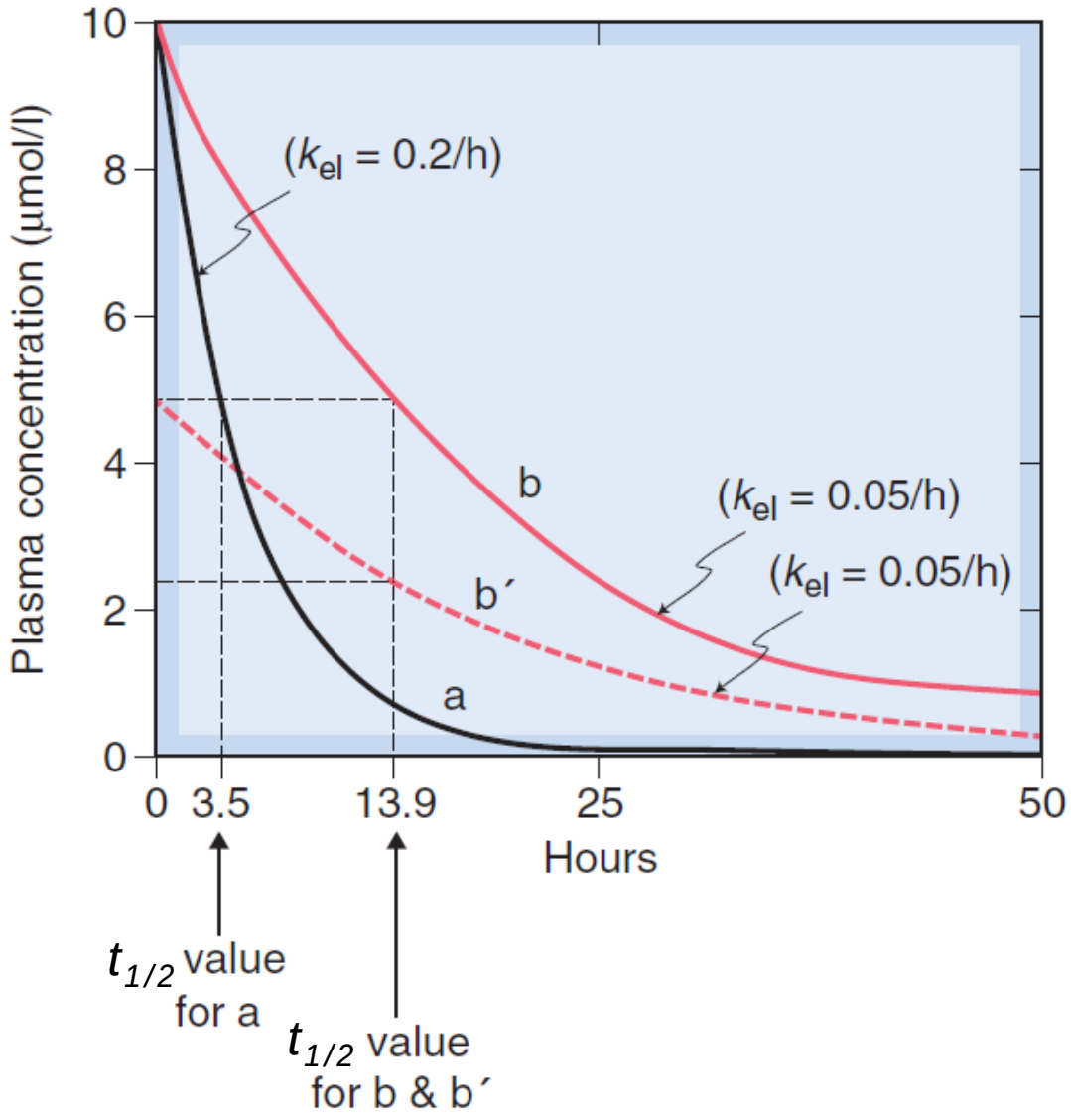
$$CL = k_{el} \times V_d$$

The volume that is cleared of drug in unit time

Excretion and metabolism together is called elimination, which can be characterized by elimination rate constant (k_{el})

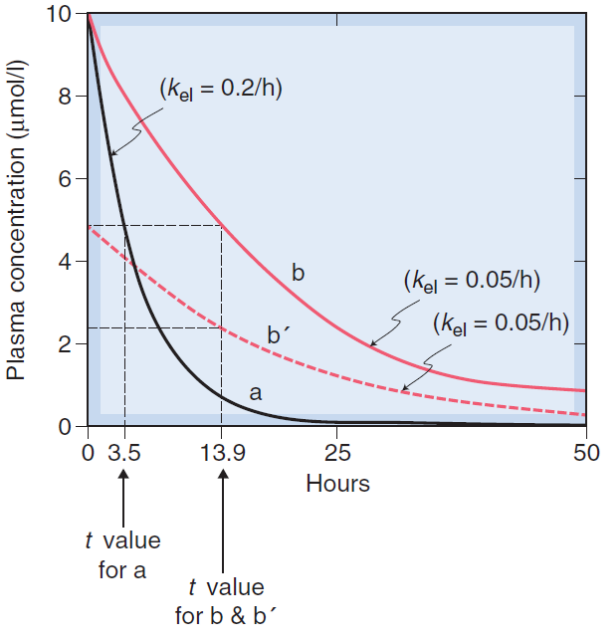
One-compartment model, single bolus *intra venous* administration



The concentration falls exponentially towards zero:
after one half-life, the concentration will have fallen to half the initial concentration; after two half-lives, it will have fallen to one-quarter the initial concentration; after three half-lives, to one-eighth; and so on.
➔ the longer the half-life, the longer the drug will persist in the body after dosing is discontinued.

Drugs **a** and **b** differ only in their elimination rate constant, k_{el}.
Curve **b'** shows the plasma concentration time course for a smaller dose of b.
Note that the half-life ($t_{1/2}$) does not depend on the dose.

One-compartment model, single bolus *intra venous* administration



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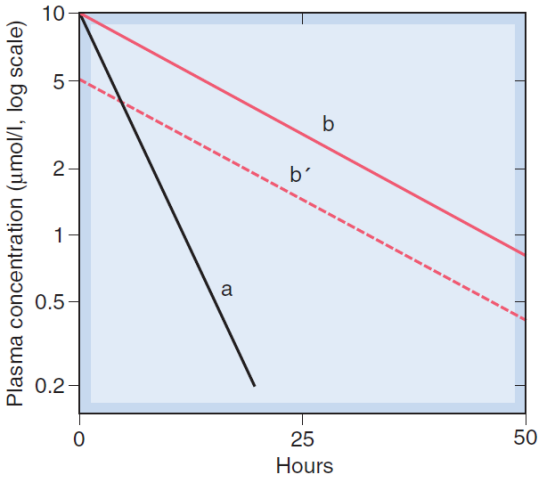
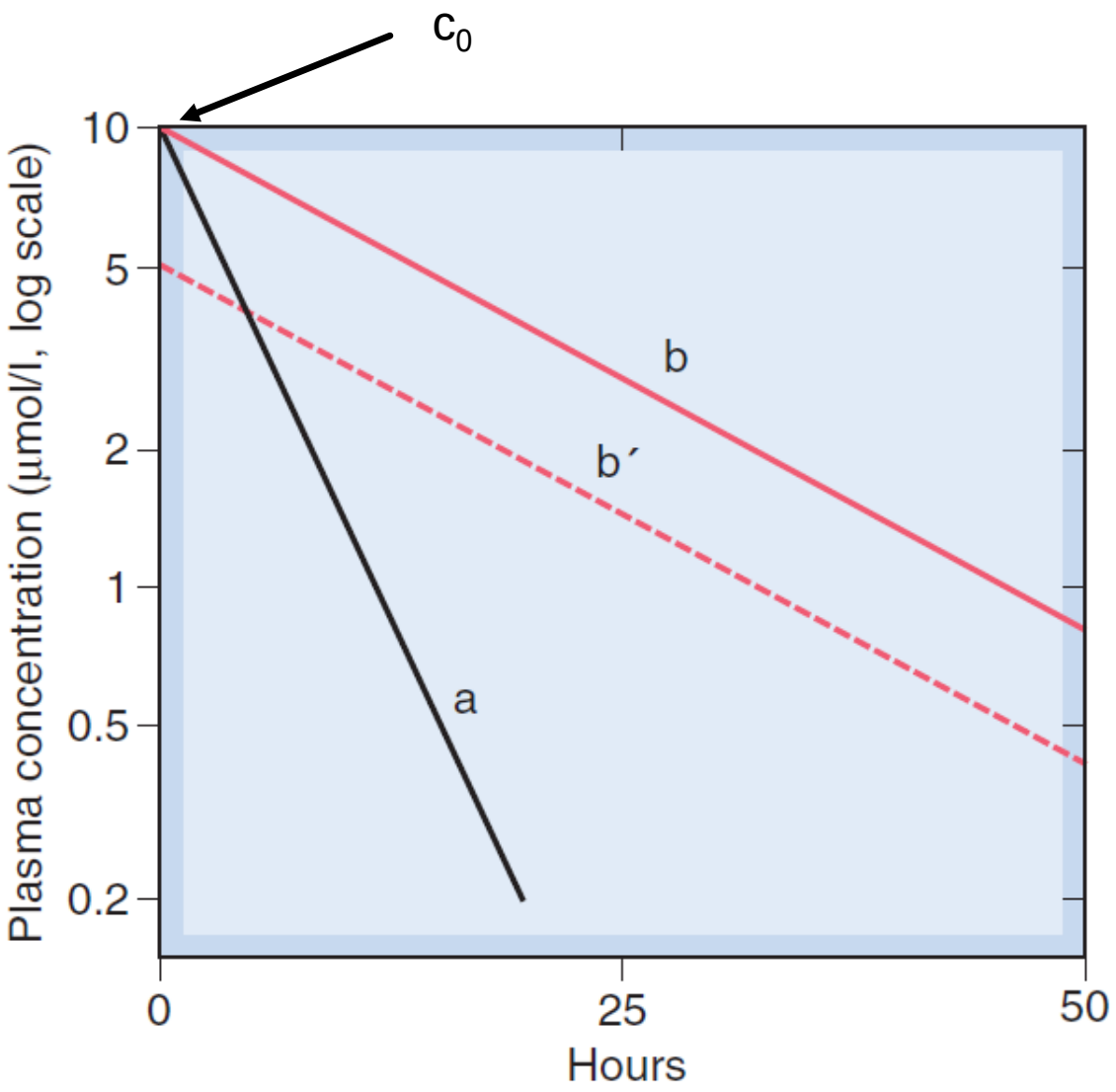


plasma concentration is plotted on a logarithmic scale

One-compartment model, single bolus *intra venous* administration



The straight line shows that concentration declines exponentially.

This is useful because:

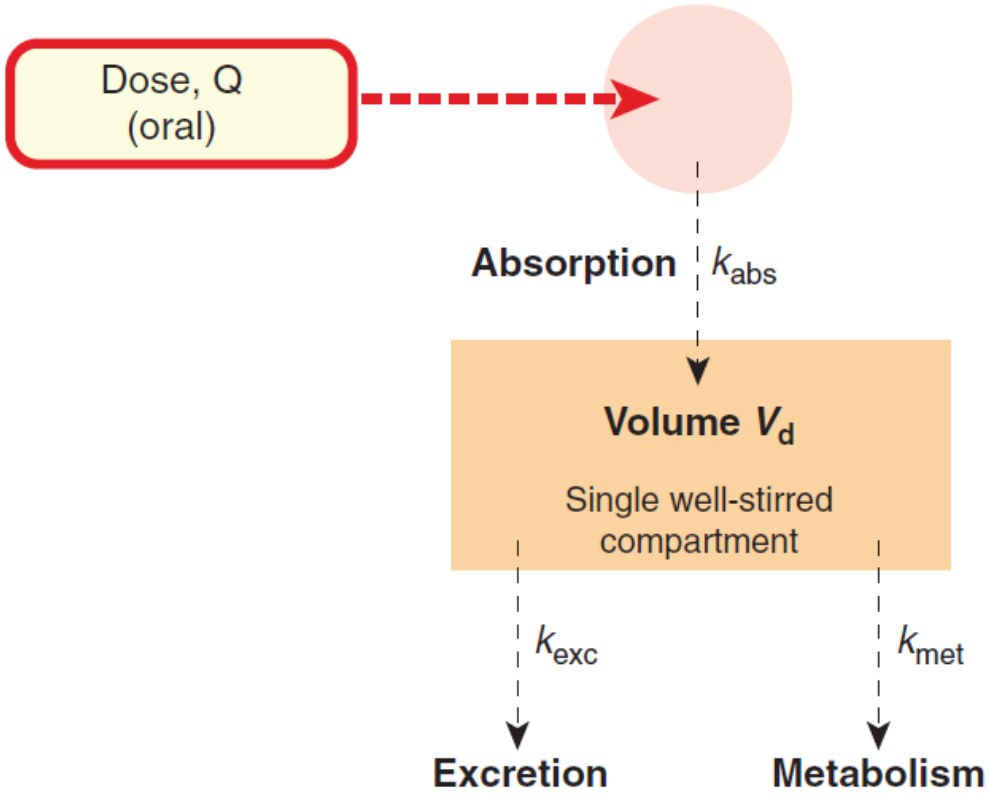
Extrapolation back to the ordinate at zero time gives an estimate of C_0, the concentration at zero time, and hence of V_d, the volume of distribution.

$$Q = c_0 \times V_d$$

The steepness of the straight line depends on the k_{el}, thus we can calculate the CL.

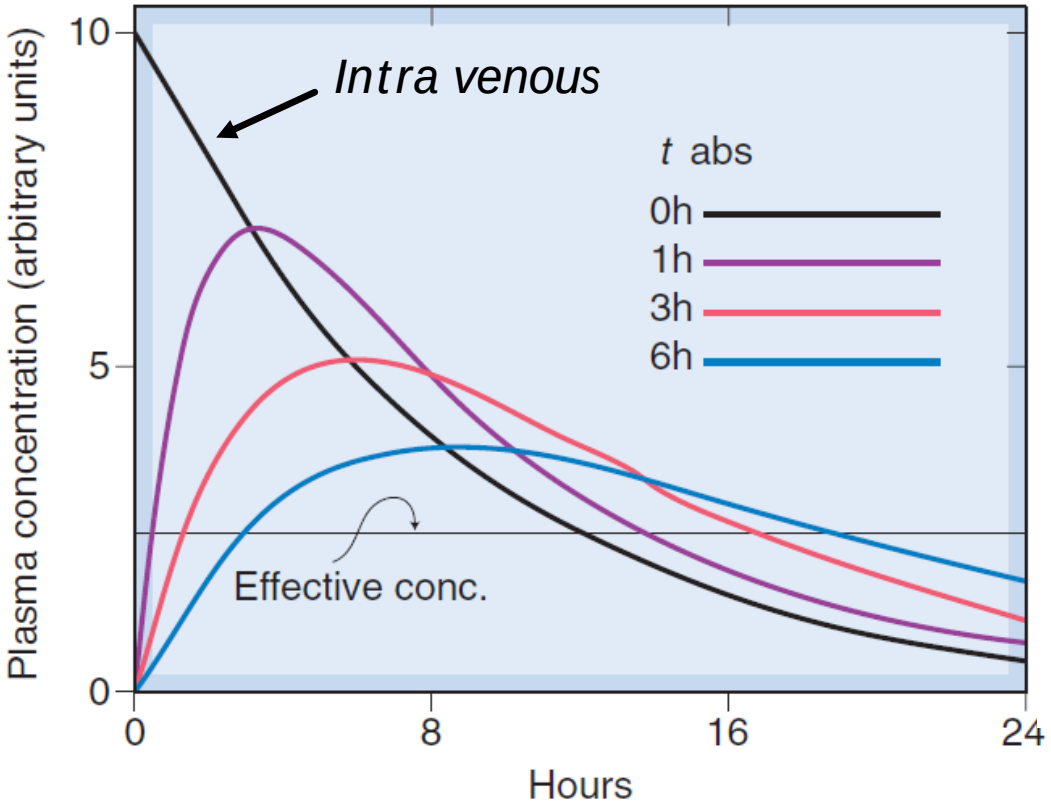
$$CL = k_{el} \times V_d$$

One-compartment model, single bolus *per os* administration



In this case absorption modifies the shape of the curve

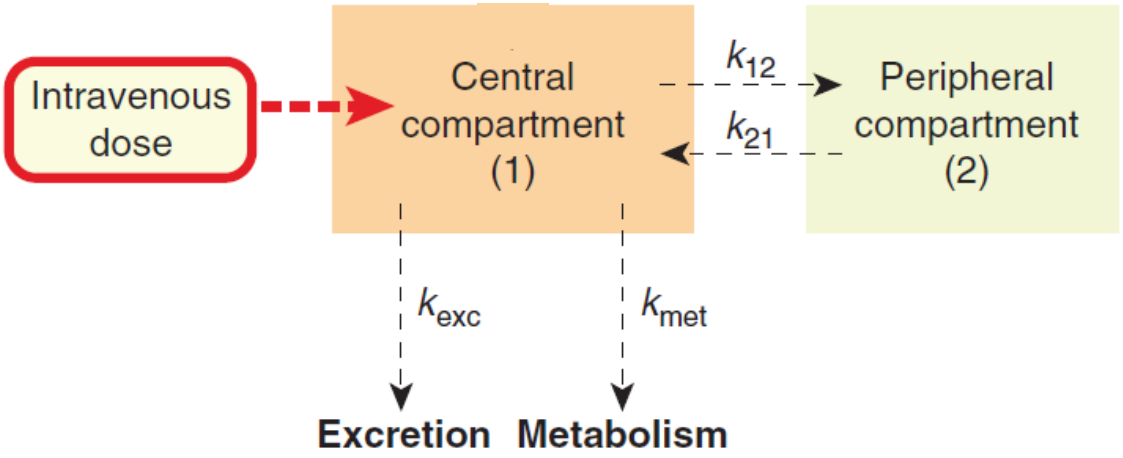
One-compartment model, single bolus *per os* administration



The elimination half-time is 6 h. The absorption half-times ($t_{1/2}$ abs) are marked on the diagram. (Zero indicates instantaneous absorption, corresponding to intravenous administration.)

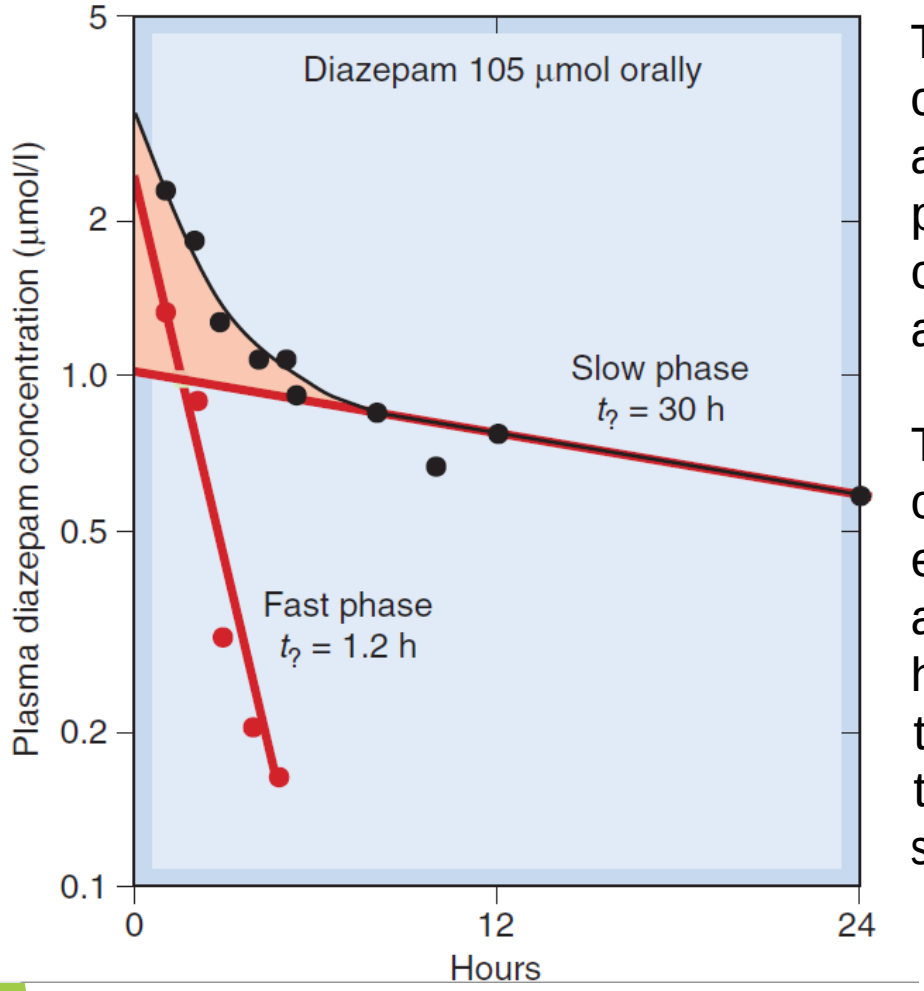
Note that the peak plasma concentration is reduced and delayed by slow absorption, and the duration of action is somewhat increased.

Two-compartment model, single bolus *intra venous* administration



The two-compartment model is a widely used approximation in which the tissues are lumped together as a peripheral compartment. Drug molecules can enter and leave the peripheral compartment only via the central compartment, which usually represents the plasma

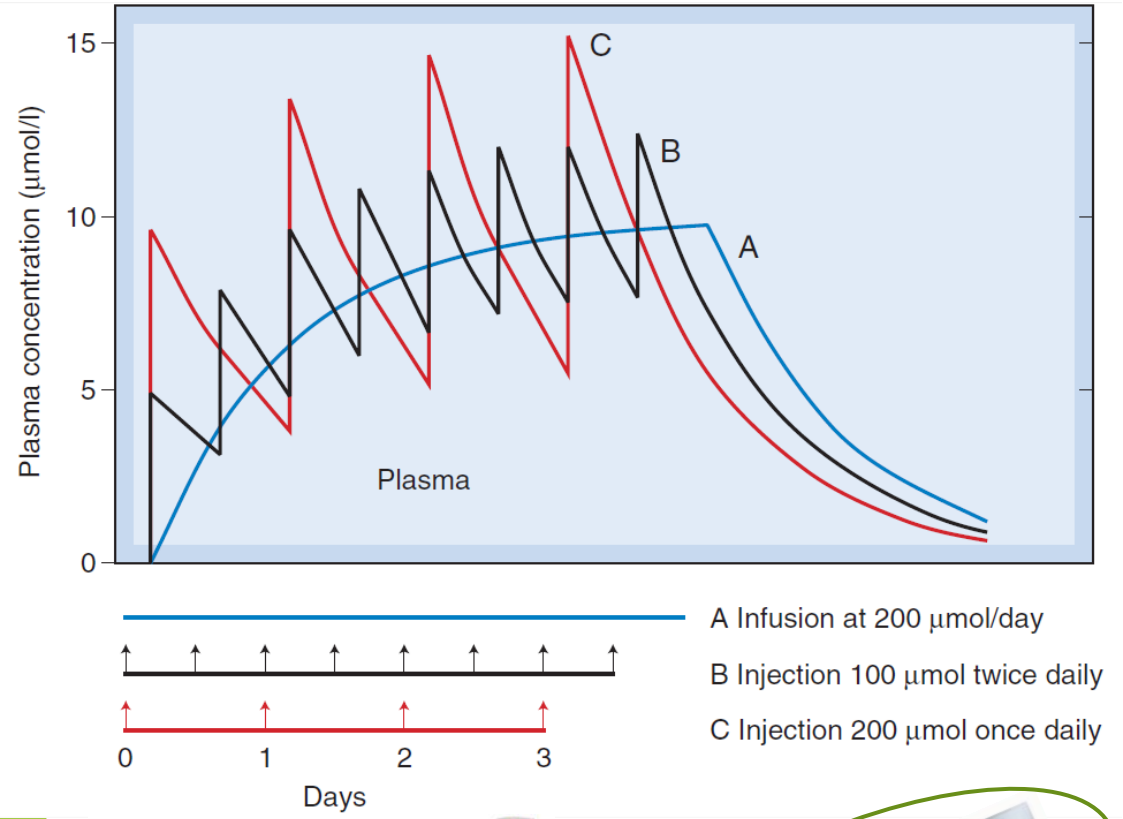
Two-compartment model, single bolus *intra venous* administration

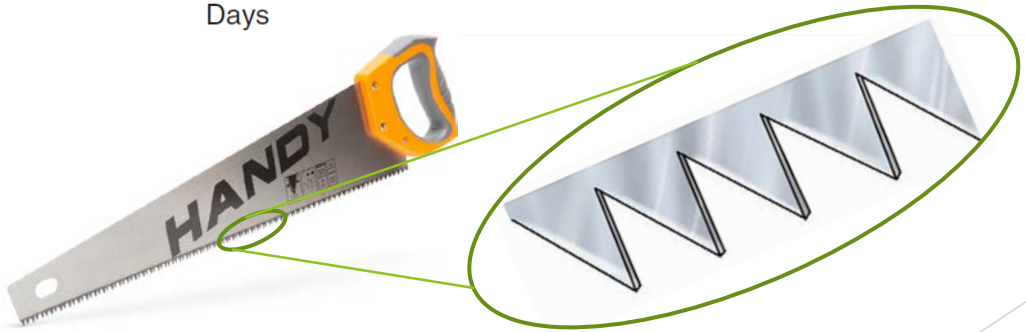


The effect of adding a second compartment to the model is to introduce a second exponential component into the predicted time course of the plasma concentration, so that it comprises a fast and a slow phase.

The graph shows a **semilogarithmic** plot of plasma concentration versus time. The experimental data (black symbols) follow a curve that becomes linear after about 8 h (slow phase). Plotting the deviation of the early points (pink shaded area) from this line on the same coordinates (red symbols) reveals the fast phase.

One compartment model, continuous *intra venous* administration





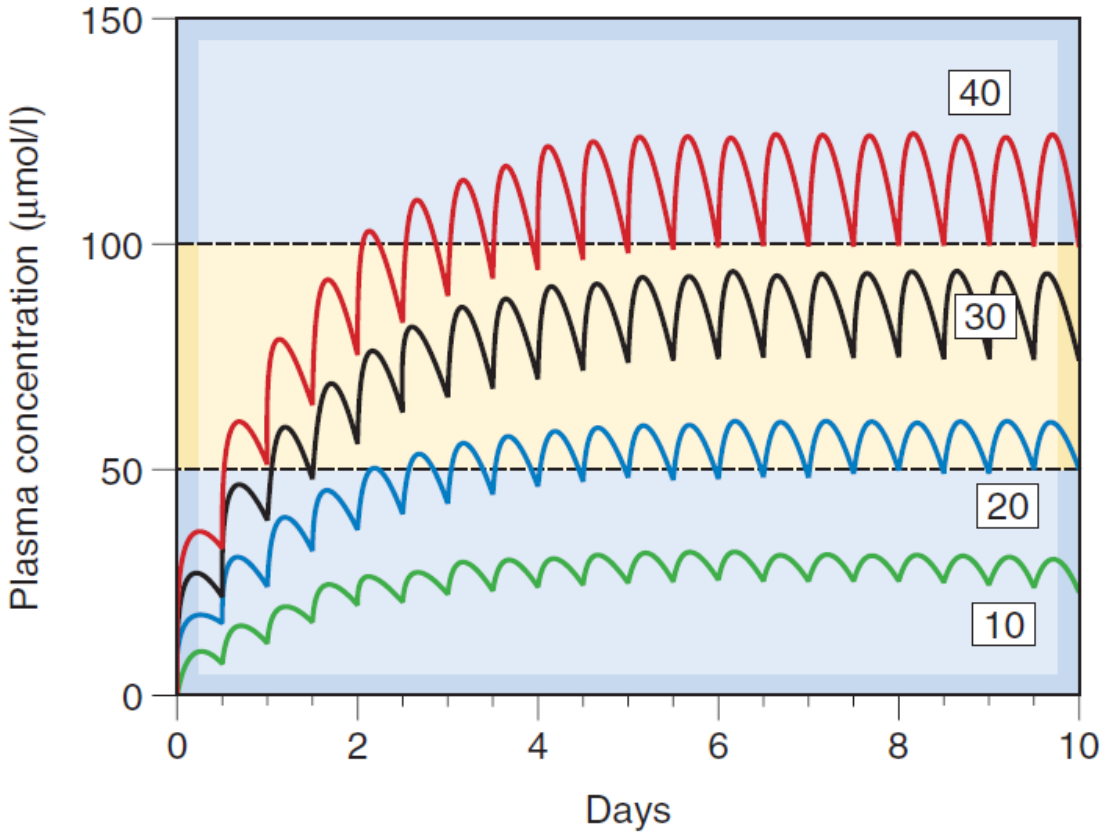
Smooth curve **A** shows the effect of **continuous infusion** for 4 days; curve **B** *the same total amount* of drug given **in eight equal doses**; and curve **C** the same total amount of drug given **in four equal doses**.

The drug has a half-life of 17 h and a volume of distribution of 20 L.

Note that

- in each case a steady state is effectively reached after about 3 days (about four half-lives), and
- that the mean concentration reached in the steady state is the same for all three schedules.

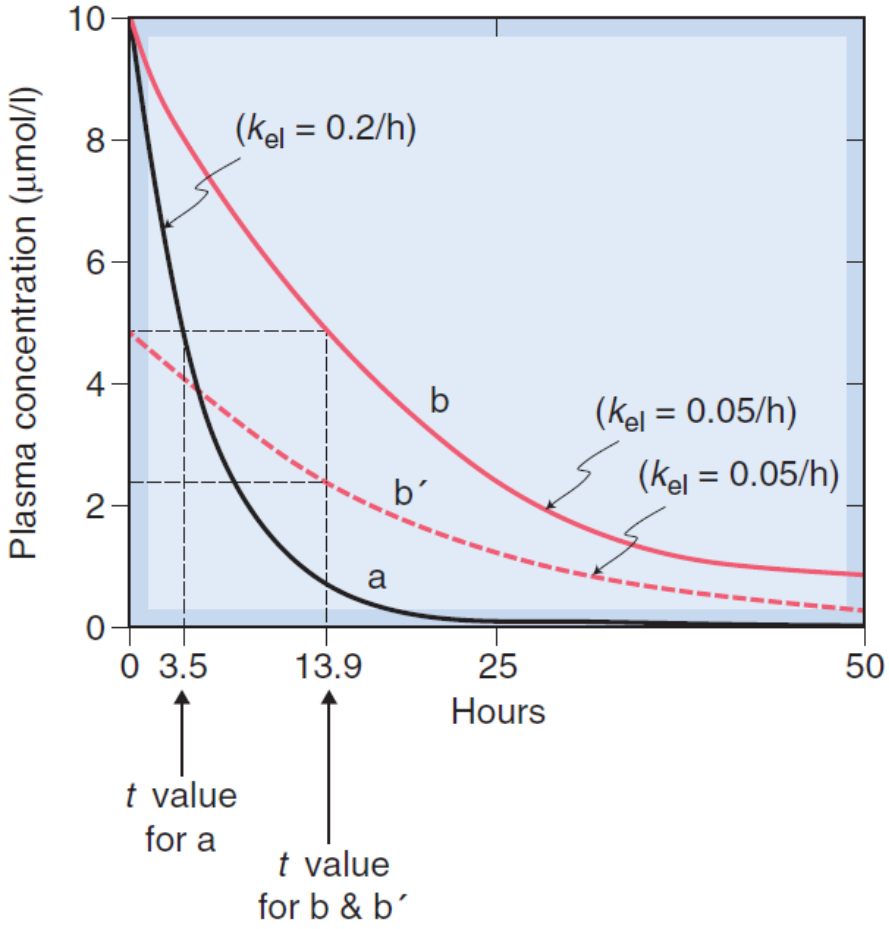
One compartment model, continuous *per os* administration



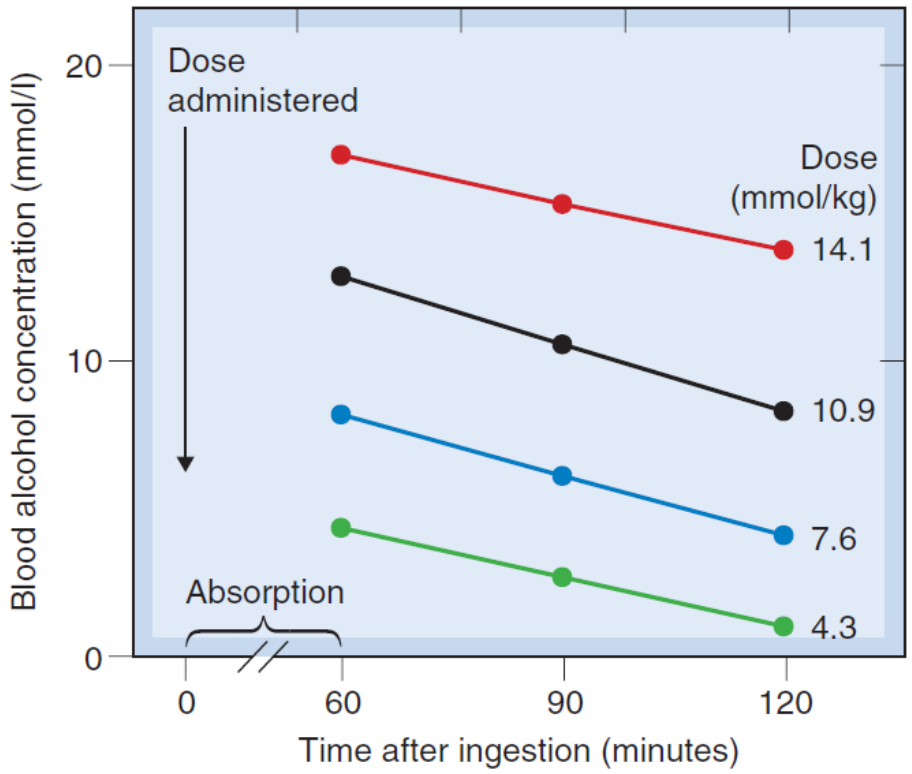
Absorption modifies the image.
In the case of higher concentrations, the steady state concentration is also higher

Zero-order / Saturation kinetics
vs
First-order kinetics (encountered this far)

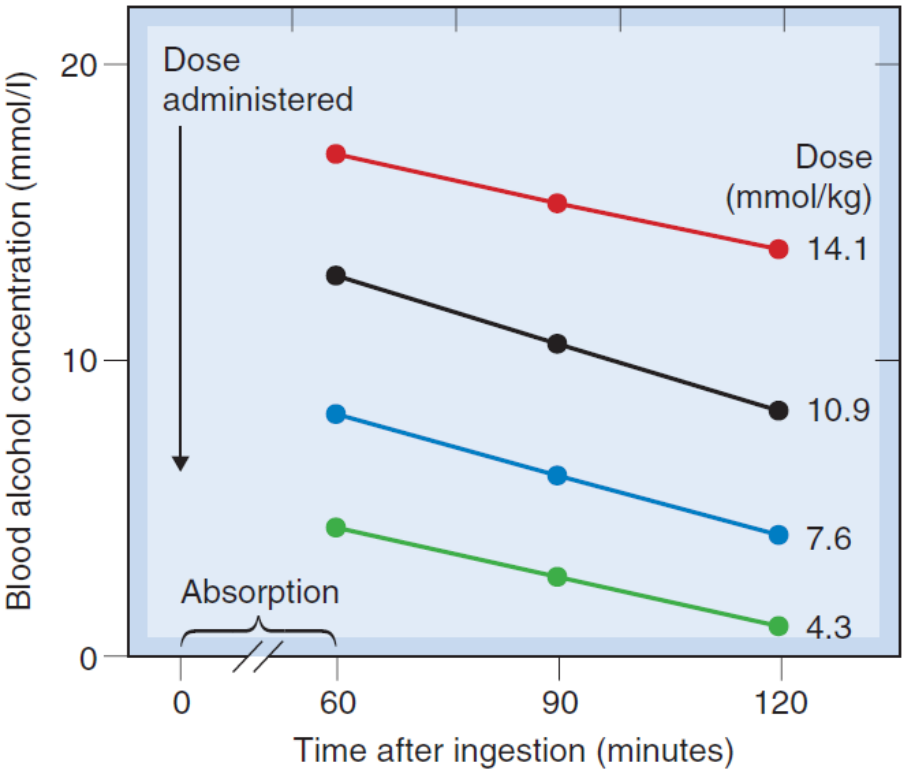
First-order kinetics



Zero-order kinetics
(This is NOT semi-logarithmic)



Zero-order/saturation kinetics

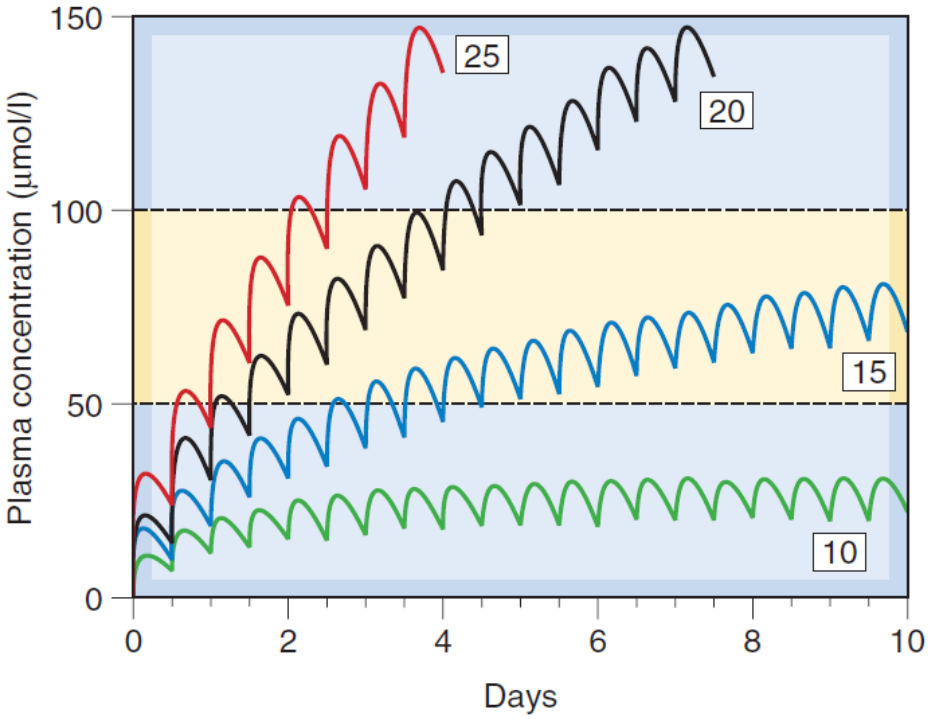


The blood alcohol concentration falls linearly rather than exponentially, and the rate of fall does not vary with dose. drug is removed at a constant rate that is independent of plasma concentration

Zero order kinetics are typical in the case of saturated metabolism ➔ the capacity of elimination is limited

Examples include: **ethanol**, **phenytoin** and **salicylate**

Zero-order/saturation kinetics



Due to limited elimination capacity:
Note that no steady state is reached with higher doses of phenytoin, and that a small increment in dose results after a time in a disproportionately large effect on plasma concentration.
The maximum rate of metabolism sets a limit to the rate at which the drug can be administered; if this rate is exceeded, the amount of drug in the body will, in principle, increase indefinitely and never reach a steady state

Examples include: **ethanol**, **phenytoin** and **salicylate**

Prescriptions for the exam

Practice

Prescribe eye drops containing 1% (w/w) of Pilocarpini hydrochloridum

- Pilocarpinum hydrochloridum 0.1g
- Solutio ophtalmica cum benzalkonio FonoVII ad 10g

Rp./

Pilocarpini hydrochloridi

centigrammata decem (g 0,10)

Solutionis ophthalmicae cum benzalkonio FoNo VII

ad grammata decem (ad g 10,0)

Misce fiat oculogutta

Detur ad vitrum fuscum guttatorium

Da sub signo veneni!

Signetur: For external use only.
Eyedrops with 1% pylocarpin.