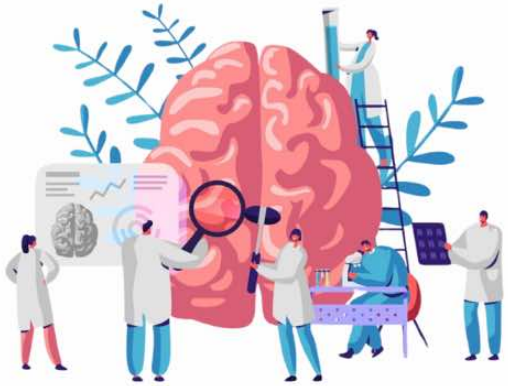


تفريغ لحاينتك

محاضرة: Ch 3

الصيدلاني\ة: Farah Aljundi

لجان الدُّفعات

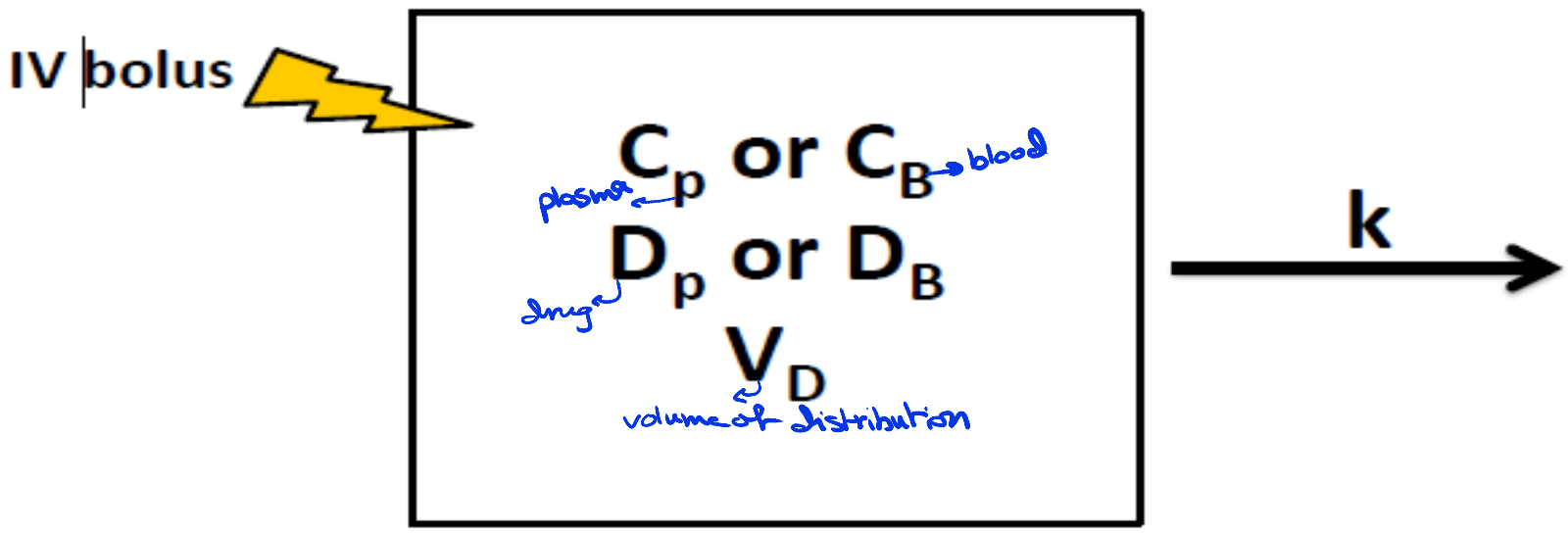
Soul Academy

One compartment open model: intravenous bolus administration

PK theory lec.3

One-compartment model

- IV bolus- One compartment model:



Open compartmental model

Cont,

- The simplest kinetic model that describes drug disposition in the body is to consider that the drug is injected all at once into a box, or compartment, and that the drug distributes instantaneously and homogenously (kinetically) throughout the compartment.

- Drug elimination also occurs from the compartment immediately after injection.

One-compartment model assumptions

Assumptions

- Rapid Mixing

drug is mixed instantaneously in blood or plasma.

- One compartment

Drug in the blood (plasma) is in rapid equilibrium with drug in the extravascular tissues.

- Linear Model

Drug elimination follows first order kinetics.

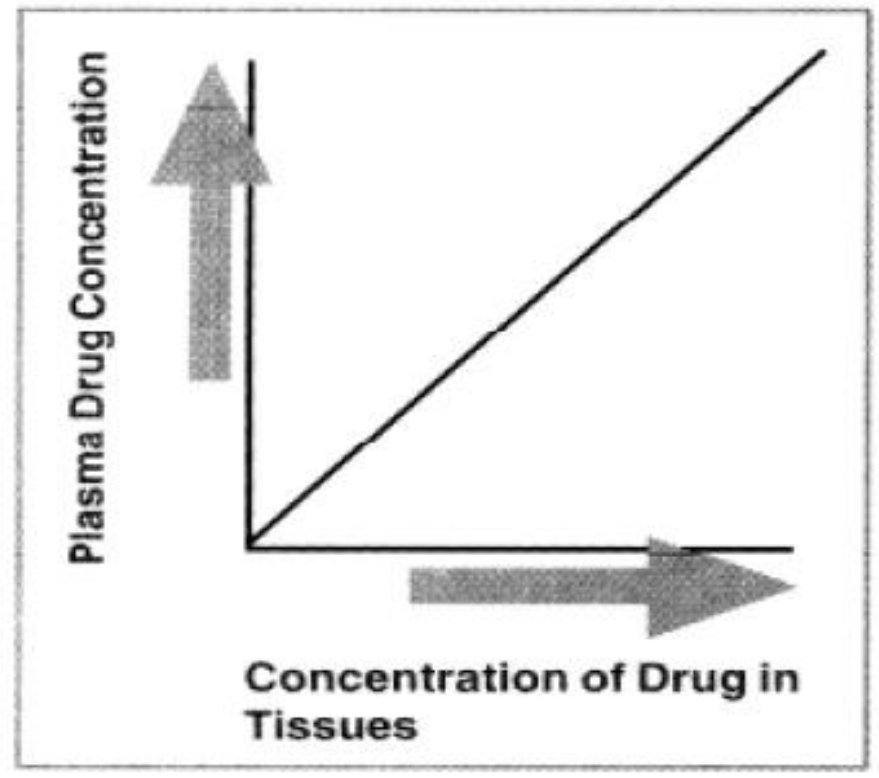


Figure 1.2. Relationship of plasma to tissue drug concentrations.

Cont,

•Changes in the plasma drug concentration reflect changes in drug concentrations in other tissues.

but proportional

•However, the plasma drug concentration does not equal the concentration at other sites but rather indicates how it changes with time.

•Generally, if the plasma concentration of a drug is decreasing, the concentration in tissues will also decrease.

Figure 1.3 is a simplified plot of the drug concentration versus time profile following an intravenous drug dose and illustrates the property of kinetic homogeneity.

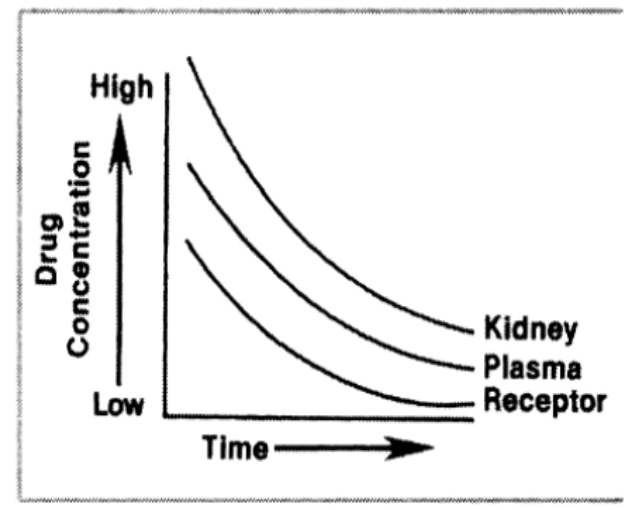


Figure 1.3. Drug concentration versus time.

Cont,

وينطبق على جميع الأدوية

•The property of kinetic homogeneity is important for the assumptions made in clinical pharmacokinetics.

• It is the foundation on which all therapeutic and toxic plasma drug concentrations are established.

• That is, when studying concentrations of a drug in plasma, we assume that these plasma concentrations directly relate to concentrations in tissues where the disease process is to be modified by the drug (e.g., the central nervous system in Parkinson's disease or bone in osteomyelitis).

•This assumption, however, may not be true for all drugs.

Linear Kinetics (First order)

Elimination rate or change in concentration is proportional to the amount available for elimination.

Glumerular Filtration } Passive

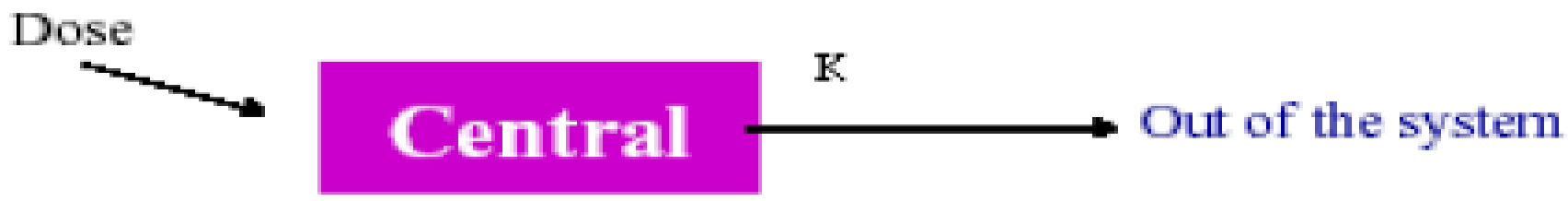
-Tubular secretion

-Biliary secretion } Involve enzymatic processes (active)

-Biotransformation

Cont,

1-Comp. Model: IV Bolus Dosing



Xt: the amount of drug remained in the compartment

K: first-order elimination rate constant (**OVERALL**) (unit = time^{-1})

$$\text{Rate of elimnation} = \frac{dX}{dt} = -KX$$

Elimination rate

Elimination rate is a first-order process

↓

The elimination is dependent on the drug concentration or amount in the body

Elimination rate constant (k):

- 1st order rate constant
- Unit: 1/time ($time^{-1}$)
- k = for all elimination processes= $k_e + k_m$ (Mainly)

$$\mathbf{k = k_e + k_m}$$

k_e : 1st order rate constant of excretion

k_m : 1st order rate constant of metabolism

Cont,

- The rate of elimination from the compartment can be calculated as

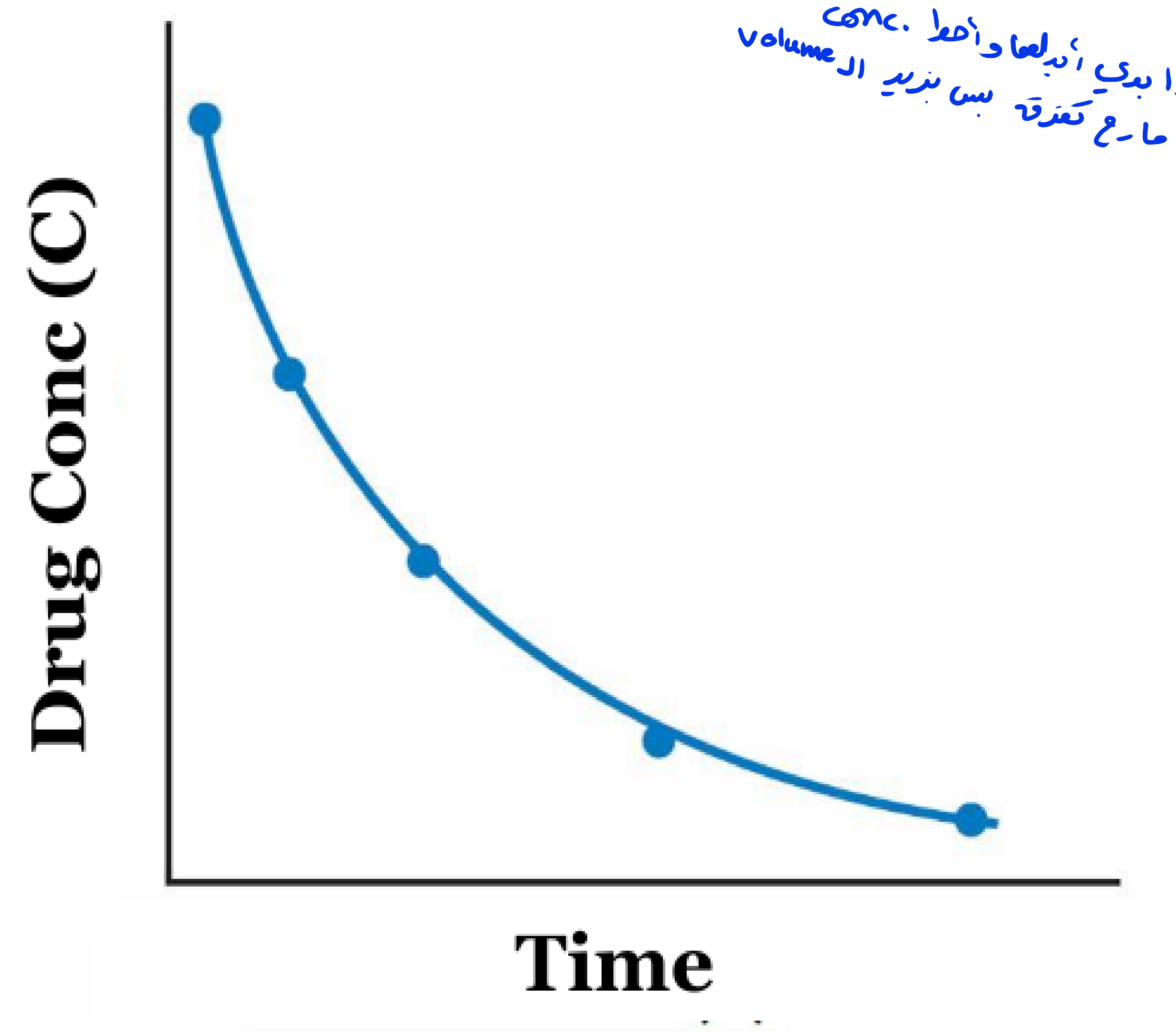
$$dD_B/dt = -k \times D_B$$

$$ln\, D_B = -k \times t + ln\, D_B{}^0 \ldots\ldots\ldots [ln]$$

$$log\, D_B = -(\frac{k}{2.303} \times t) + log\, D_B{}^0 \ldots\ldots\ldots [log]$$

$$D_B = D_B{}^0 \times e^{-kt} \ldots\ldots\ldots [e]$$

One compartment open model



إذا بدي أبدلها وأحط conc.
بس بزيد الـ volume ما رح تفرق

amount (drug)

$$C = \frac{D}{Vd} e^{-K \cdot t}$$

C= concentration

D= dose

Vd: Volume of distribution

K: elimination rate constant

t: time

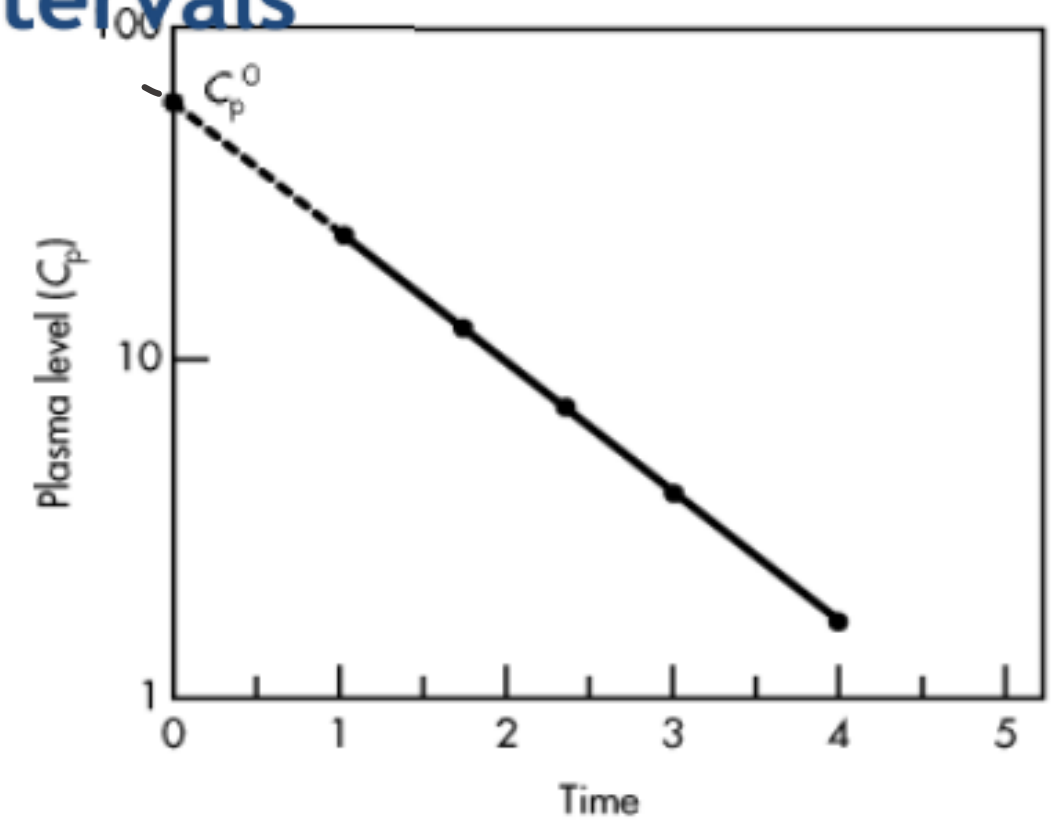
Calculation of concentration at different time intervals

- If the first plasma concentration is taken at t_1 instead of at zero and corresponds to plasma drug concentration C_1, then C_2 is the concentration at time t_2 and t is set to $(t_2 - t_1)$ Then:

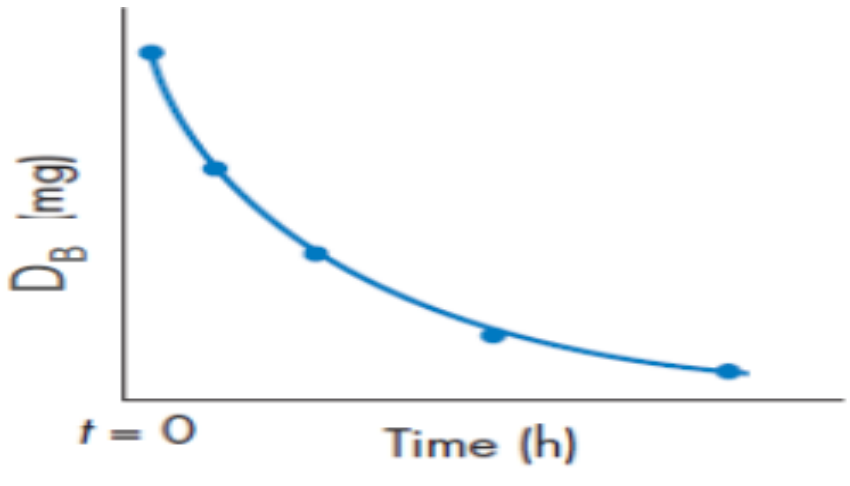
$$C_2 = C_1 * e^{-k(t_2 - t_1)}$$

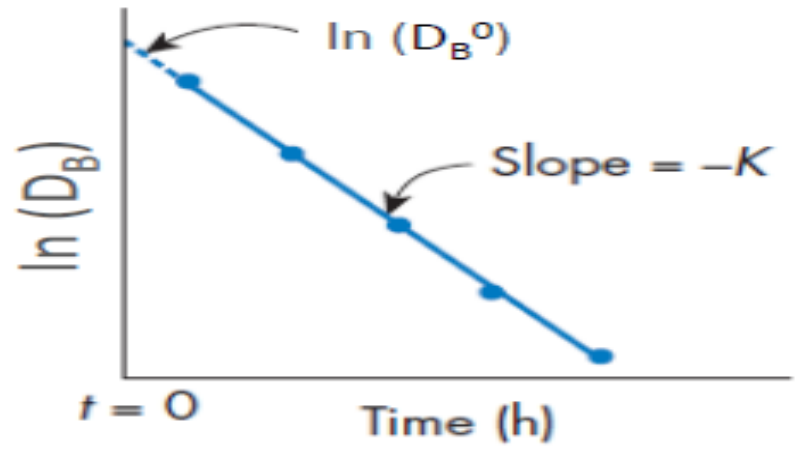
slope = $\frac{\Delta y}{\Delta x}$

$$\ln C_2 = \ln C_1 - k(t_2 - t_1) \quad - k = \frac{\ln C_2 - \ln C_1}{(t_2 - t_1)}$$



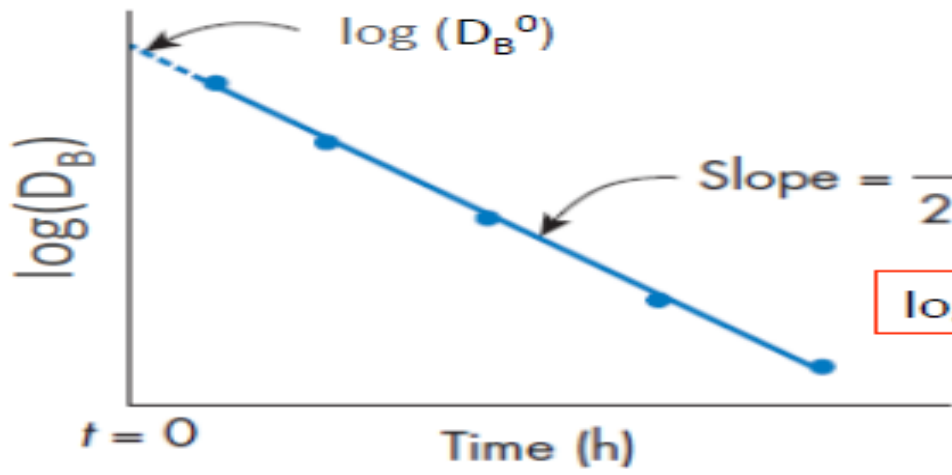
First order kinetic graphs





$D_B = D_B^o * e^{(-kt)}$

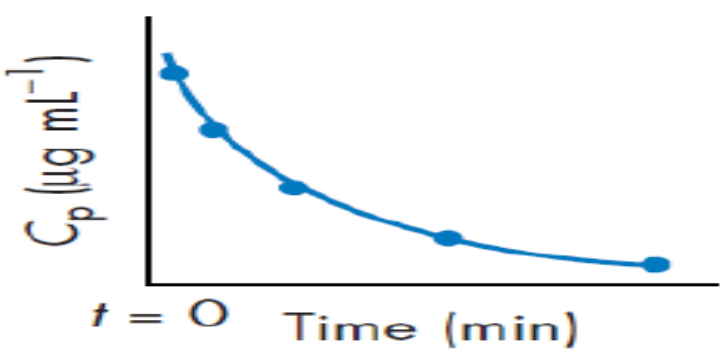
$\ln D_B = - k*t + \ln D_B^o$



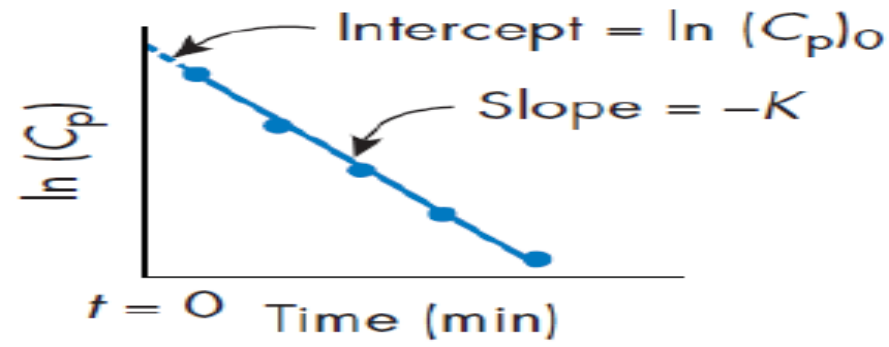
$\log D_B = - (k*t/2.303) + \log D_B^o$

- As we usually take samples from the plasma or blood → then the results are in concentration units not mass units
- So we will have V_D and C_p →

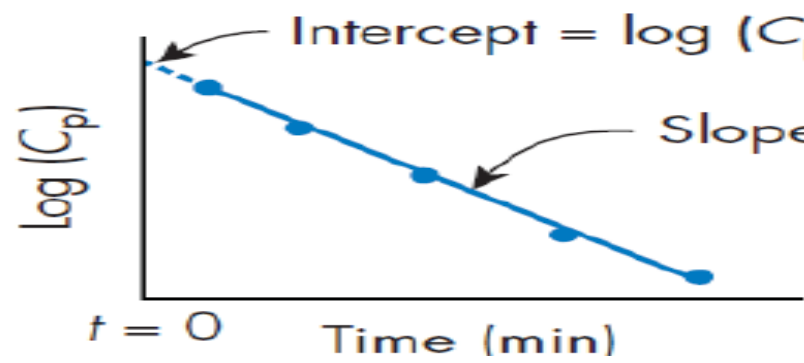
$$D_B = V_D * C_p$$



$C_p = C_p^o * e^{(-kt)}$

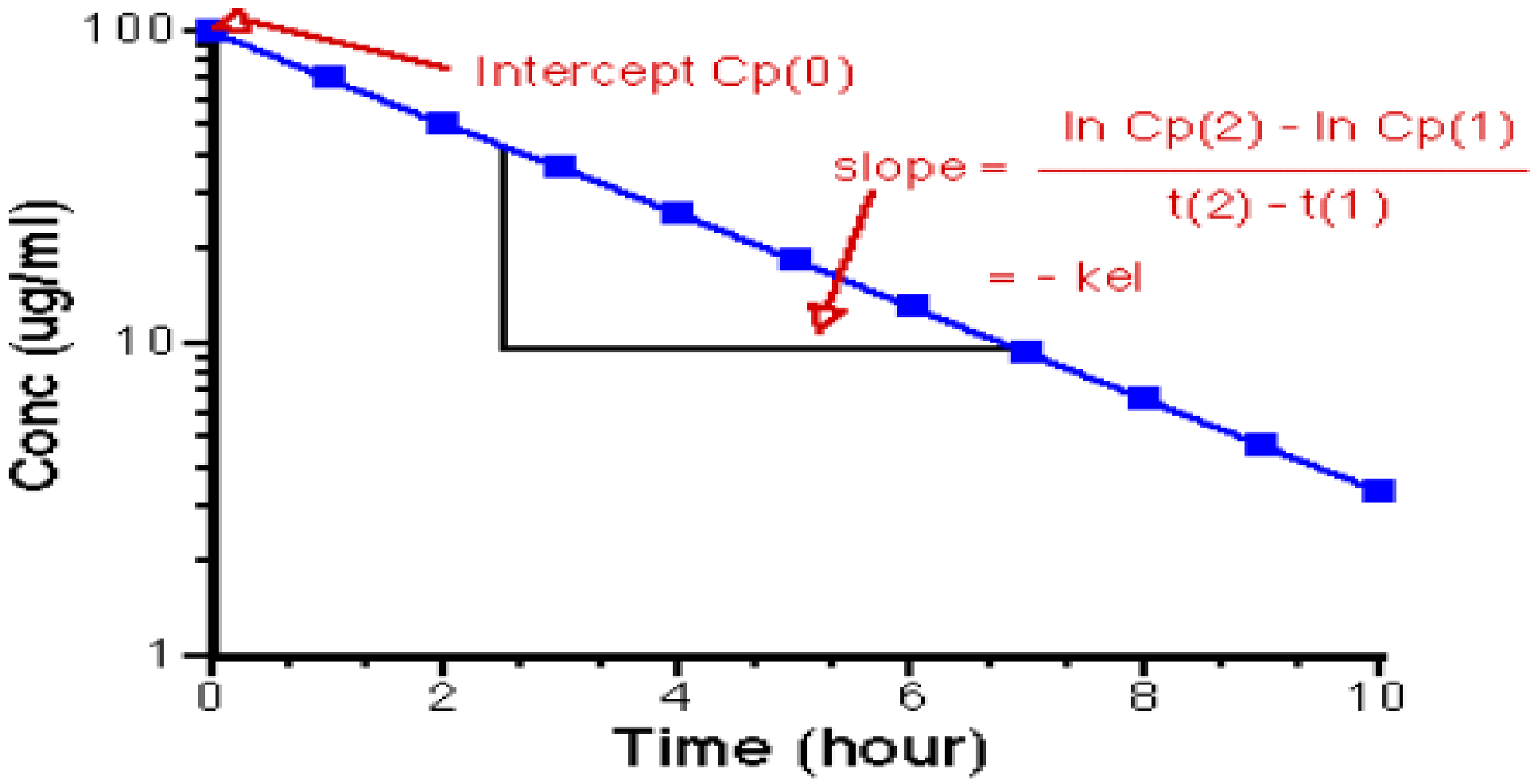


$\ln C_p = - k*t + \ln C_p^o$



$\log C_p = - (k*t/2.303) + \log C_p^o$

Determination of K



example

Practice questions

- Drug X has an elimination rate constant of 0.173 hr^{-1} ; 5 mgs of the drug were administered as an IV bolus. Calculate the following
- A) The drug amount after 2 hours
- B) The rate of reaction after 2 hours

First order, 0.173 = K ; 5 mgs = A_0

$K = 0.173\ hr^{-1}$, $t = 2\ hr$

$A_0 = 5\ mg$

ⓐ $A_{(t=2)} = A_0 * e^{-Kt}$

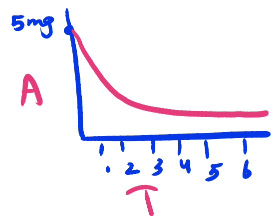
$\ln A = \ln A_0 - Kt_{(2)}$

$\ln A = \ln 5 - 0.173 \times 2$

$\ln A = 1.6 - 0.346$

$\ln A = 1.254$

$A = 3.49\ mg$



$t_{1/2} = 0.693/K$

$= 0.693/0.173$

$t_{1/2} = 4$ ← يفترض إنه بعد 4 ساعات تكون ال amount نزل للنص من 5mg إلى 2.5mg

معناها 4 لما لطلبوني أحسب A بعد 2hr أكيد رح تكون أعلى من 2.5 mg وأقل من 5mg.

* small Hint

rate of reaction (elimination rate) — هاي غير elimination rate constant → K

Ⓑ $\frac{dA}{dt} = -KA_{(t=2)}$

$= -0.173 * 3.49$

$= -0.6\ mg/hr$

* إذا قلك rate of reaction تكتبه = $-0.6\ mg/hr$ (declining — عشان نعرف انه ال rate)
* إذا قلك rate of elimination تكتبه = $0.6\ mg/hr$ (القيمة المطلقة)
* إذا قلك elimination rate constant تكتبه = $K = 0.173\ hr^{-1}$

PK parameters

Fundamental parameters in one compartment

non fundamental parameter → AUC

- Apparent Volume of Distribution (Vd)
- Elimination rate constant (K)
- Elimination half life ($t_{1/2}$)
- Clearance (Cl)

Apparent Volume of Distribution (Vd)

- •This apparent volume of distribution is not a physiological volume. It won't be lower than blood or plasma volume but it can be much larger than body volume for some drugs.

•It is a mathematical factor relating the amount of drug in the body and the concentration of drug in the measured compartment, usually plasma:

$$V_d = \frac{\text{AMOUNT of drug in the body}}{\text{CONCENTRATION in plasma}}$$

- Vd: A measure of the tendency of a drug to move out of the blood plasma to some other site.

Cont,

- Concentrations (mass per unit volume or amount per unit volume), not masses (mg or µg), are usually measured in plasma or serum (more often than blood).
- Therefore, a term is needed to relate the measured concentration (Cp) at a time to the mass of drug (X) at that time. This term is defined as the apparent volume of distribution (V).
- The apparent volume of distribution (V) is simply a proportionality constant whose sole purpose is to relate the plasma concentration (Cp) and the mass of drug (X) in the body at a time. **It is not a physiological volume**

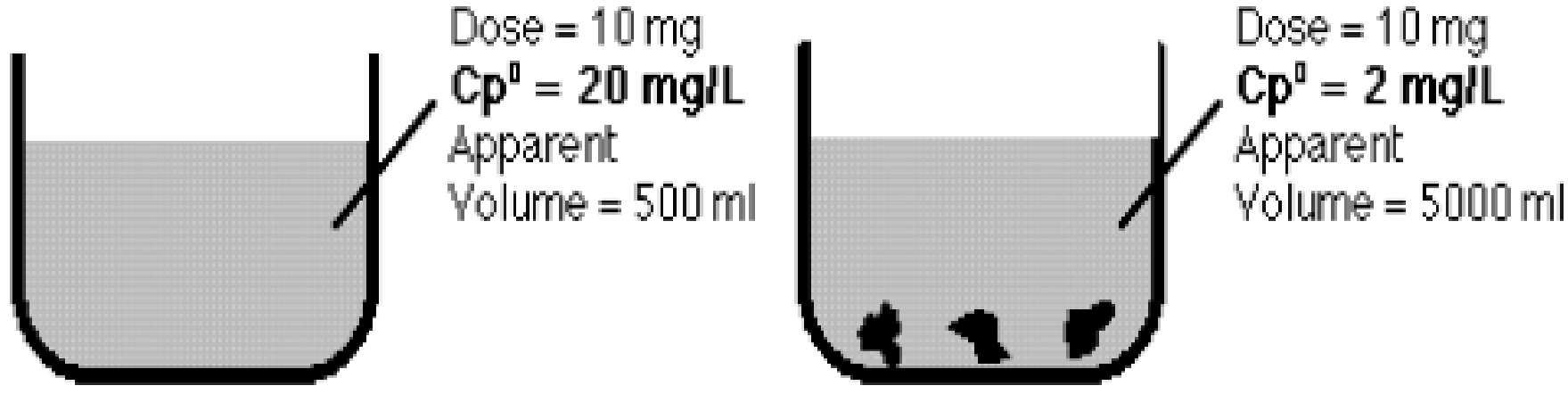
$$Vd = \frac{\text{dose}}{\text{initial conc.}} = \frac{X_0}{C_0}$$

Factors Affecting Drug Distribution:

- **Rate of distribution**
  - ✓ Membrane permeability
  - ✓ Lipid Solubility
  - ✓ pH - pKa (pH-partition theory for ionizable molecules)
  - ✓ Blood perfusion of organs and tissues
- **Extent of Distribution**
  - ✓ Plasma protein binding
  - ✓ Intracellular binding

Volume of distribution

$$\textbf{Definition:}\quad V = \frac{\text{amount of drug in the body}}{\text{concentration measured in plasma}}$$



Cont,

The more the drug penetrate into tissues/organs following the administration of the dose, the smaller will be the plasma and/or serum drug concentration→→

Therefore the higher is the hypothetical volume into which the drug is distributed

- **V_D is usually a property of a drug rather than of a biological system:** the extent to which certain drug is distributed in the body tissues

Cont,

- Reflects the extend of drug distribution in the body tissues and organs

↑ drug distribution → ↑ V_D

e.g.

- Highly protein bound or highly water soluble drugs → ↓ distribution → ↓ V_D
- Drugs accumulated in adipose tissues → ↑ V_D

- Reflects the lipophilicity of a drug

↑ drug lipophilicity → ↑ V_D

↑ drug hydrophilicity → ↓ V_D

List of volume of distribution of some drugs

Volume of Distribution

(Volume of distribution coefficient) وحدة هاي * معامل الـ Vd

وحدة الـ volume ← volume هاي مش وحدة (يوم)* (L) أو (ml) كالها بعده اشي بجانبها

Erythropoietin	5 L	0.07 L/kg*
Warfarin	8 L	0.12 L/kg*
Phenytoin	45 L	0.63 L /kg*
Digoxin	500 L	7 L /kg*
Amiodarone	5000 L	70 L /kg*
Chloroquine	15000 L	215 L/kg*
Quinacrine	35000 L	500 L/kg*

* ليه kg ؟
الدفع الطبيعي لما نجيب قسمت وزنه الانسان بفترض إنه وزنه 70kg

مثلاً :
$\frac{500\,L}{kg} \times 70\,kg = 35000\,L$

untimalarials

يعني هاد الكلام ← كمية قليلة جدًا الي بضل موجود بالدم ، الباقي كله عم يروح disposition

* Distribution Coefficient

Clearance ← $Cl = K \cdot Vd$

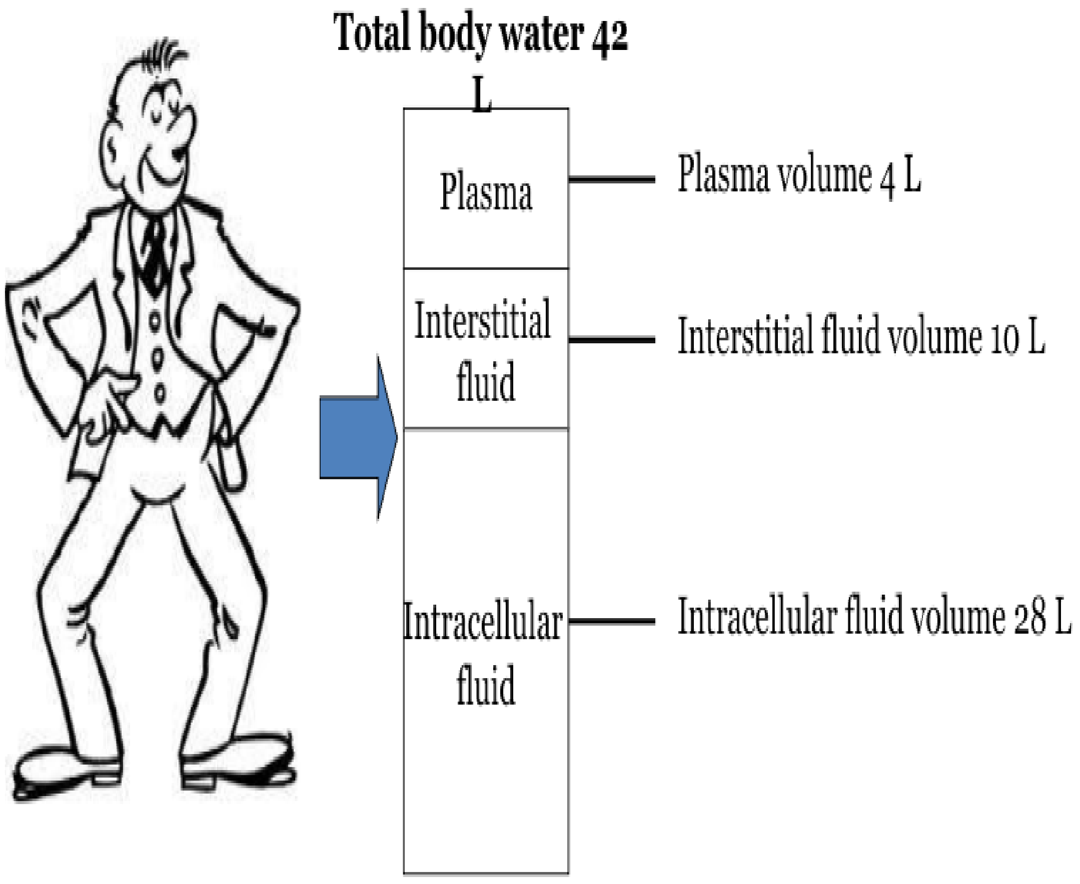
Cl ?

$V = 2\,L/kg \rightarrow 2 \times 70 = 140\,L$

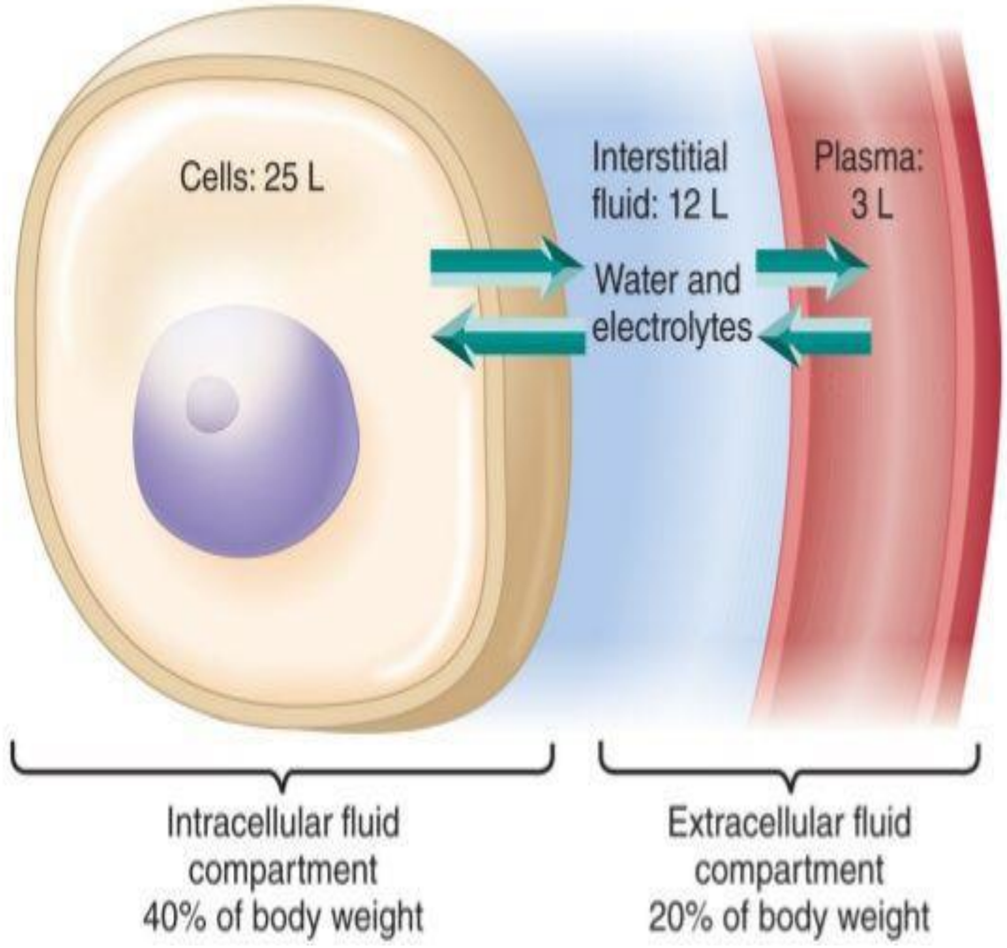
$K = 0.1$

$Cl = 0.1 * 140 = 14\,L/hr$

The real Volume of Distribution has physiological meaning and is related to body water



Major fluid compartments in the body



لو عنا مريض إنو الوزن
70 kg
منه Fluid
60%
42 L

40% ICF → 28 L ← تكون already توزع ECF معناها توزع بكل الجسم

20% ECF → 14 L

- 3 - 4 L plasma
- 10 - 11 L ISF

plasma ← مثال: heparin , ال dyes الي بستخدموها في ال angeograph
(عشان لازم يكونوا high M.W + highly hydrophilic)

- إذا بدي الدواء يكون في البلازما ← high MW + highly hydro
- إذا بدي إياه يتوزع في ECF بدون ICF ← بخليه hydrophilic ولكن نقلل M.W عشان يقدر يدخل من خلال ال junctions
  ← معناها Vd إله أكثر من 3-4 لحد 14 L . إذا كان فوق 14 بيشري أنا ضامنة إنو دخل ICF .
- إذا بدي إياه ICF ← lipophilic + low M.W
  وبالتالي تركيزه يكون ص

Apparent Volume of Distribution

- If a drug has a high molecular weight or is extensively protein bound, it is too large to pass through the slit junctions of the capillaries and, thus, is effectively trapped within the plasma (vascular) compartment. As a result, it has a low Vd that approximates the plasma volume, or **about 4 L in a 70-kg** individual (e.g. Heparin).
- If a drug has a low molecular weight but is hydrophilic, it can pass through the endothelial slit junctions of the capillaries into the interstitial fluid. However, hydrophilic drugs cannot move across the lipid membranes of cells to enter the intracellular fluid. Therefore, these drugs distribute into a volume that is the sum of the **plasma volume and the interstitial fluid**, which together constitute the extracellular fluid, (about 20% of body weight or 14 L in a 70-kg individual) (e.g. aminoglycoside antibiotics)

Apparent Volume of Distribution

- If a drug has a low molecular weight and has enough lipophilicity, it can move into the interstitium through the slit junctions and pass through the cell membranes into the intracellular fluid. These drugs distribute into a volume of about 60% of body weight or about 42 L in a 70-kg individual. *Ethanol* exhibits this apparent Vd.

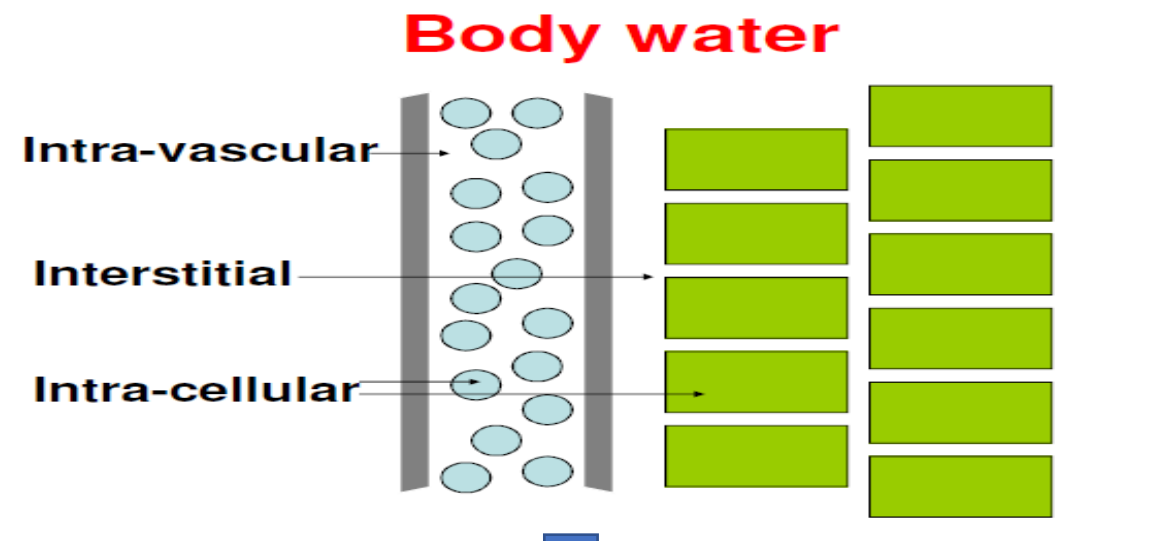
- In general, a larger Vd indicates greater distribution into tissues; a smaller Vd suggests confinement to plasma or extracellular fluid.

Vd coefficient

Drug X has a volume of distribution of 20 L/kg, what does this mean?

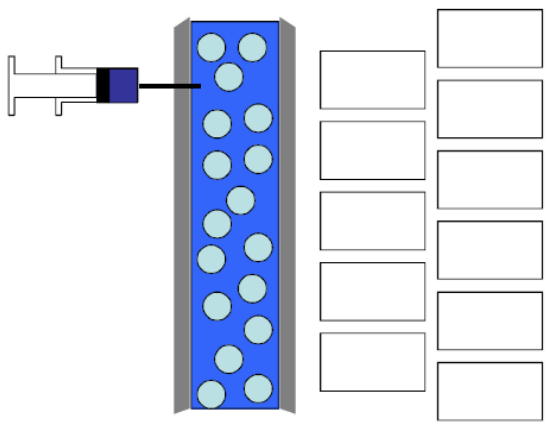
Volume of distribution

- The apparent volume of distribution has a minimum value that is dependent on physiological factors. A drug must be distributed at least throughout the plasma. Therefore, the minimum value of the apparent volume of distribution should be at least 3–4 L in a healthy 70 kg subject.
- There is theoretically, however, no upper limit. The higher the tissue affinity, the lower the fraction of drug will be in plasma.
- Theoretically, if the plasma concentration approaches a value of zero at infinitely high tissue affinities, the value of the volume of distribution moves towards infinity. ∞



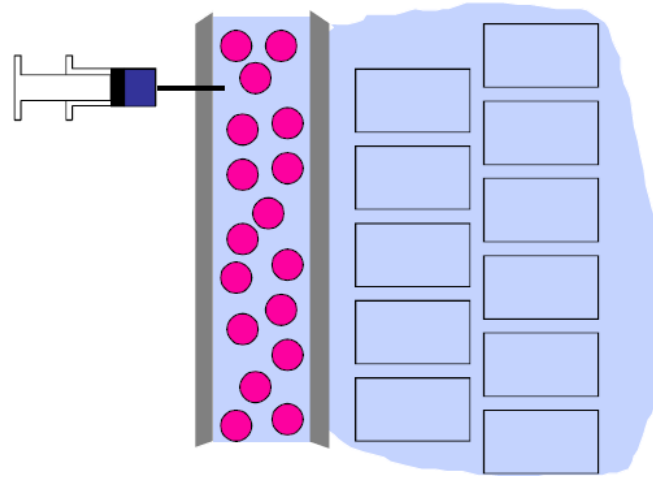
Distribution - Evan's Blue

Intra-vascular space only



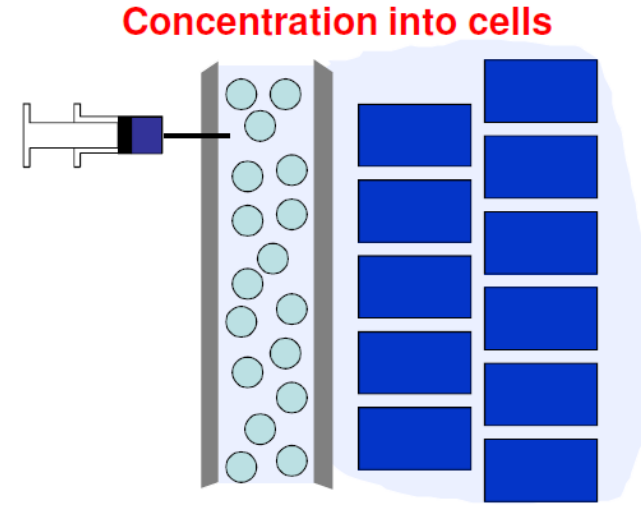
Distribution - Ethanol aminoglycoside

All water



Distribution - Quinacrine

Concentration into cells



Apparent volume of distribution estimation

1. Plot log(C) vs. time

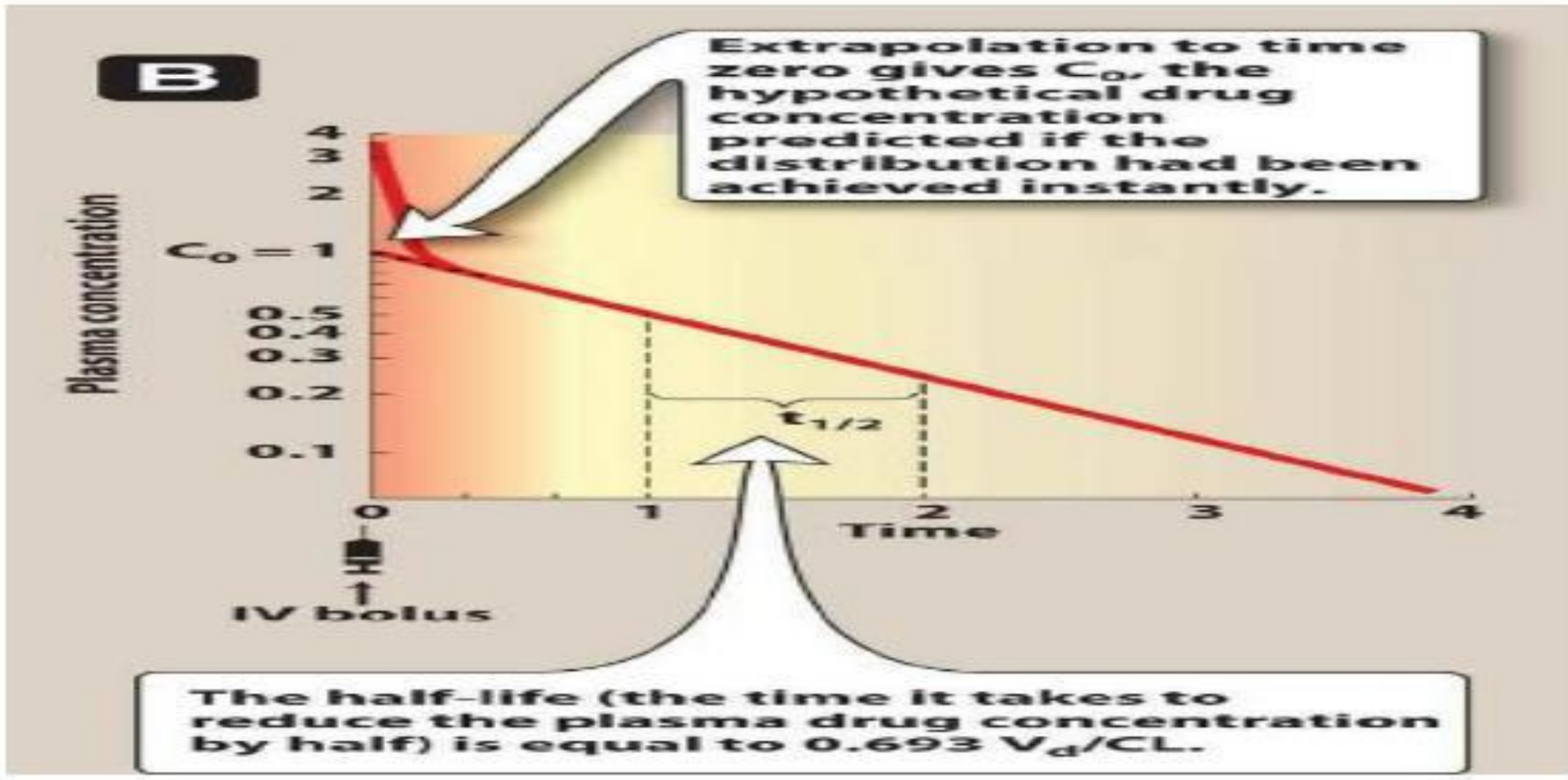
2. Plot the best-fit line

3. Extrapolate to the Y-axis intercept (to estimate initial concentration, C_0)

Vol. = amount / conc.

4. Estimate Vd: $$Vd = \frac{\text{dose}}{\text{initial conc.}} = \frac{X_0}{C_0}$$

Apparent Volume of Distribution: Mathematics



Cont,

• In a one-compartment model (IV administration), the *V*D is calculated with the following equation:

$$V_D = \frac{\text{Dose}}{C_p^0} = \frac{D_B^0}{C_p^0}$$

• When *C*p0 is determined by extrapolation, *Cp0* represents the instantaneous drug concentration after drug equilibration in the body at $t = 0$.

• The dose of drug given by IV bolus (rapid IV injection) represents the amount of drug in the body, *D*B 0 , at $t = 0$. Because both *D*B 0 and *Cp0* are known at $t = 0$, then the

$$\frac{dD_B}{dt} = -kD_B$$

the second pharmacokinetic nonfundamental parameter

Extracting AUC

المساحة تحت المنحنى

$$\frac{dD_B}{dt} = -kD_B$$

Substituting $D_B = V_D C_p$ into the previous Equation, the following expression is obtained: : AUC حوانيه -

$$\frac{dD_B}{dt} = -kV_D C_p$$

$$dD_B = -kV_D C_p dt$$

$$\int_0^{D_0} dD_B = -kV_D \int_0^{\infty} C_p dt$$

1 $AUC = \frac{D_0}{K * V_d}$

2 $AUC = \frac{C}{K}$

Volume of distribution vs AUC

The integral $\int_0^\infty C_p dt$ represents the AUC_0^∞, which is the summation of the area under the curve from $t = 0$ to $t = \infty$. Thus, the apparent V_D may also be calculated from knowledge of the dose, elimination rate constant, and the area under the curve (AUC) from $t = 0$ to $t = \infty$. This is usually estimated by the trapezoidal rule (see Chapter 2). After integration, Equation 4.12 becomes

$$D_0 = kV_D[AUC]_0^\infty$$

which upon rearrangement yields the following equation:

$$V_D = \frac{D_0}{k[AUC]_0^\infty} \tag{4.13}$$

Failure is the key
to SUCCESS.
Each mistake
teaches us something.