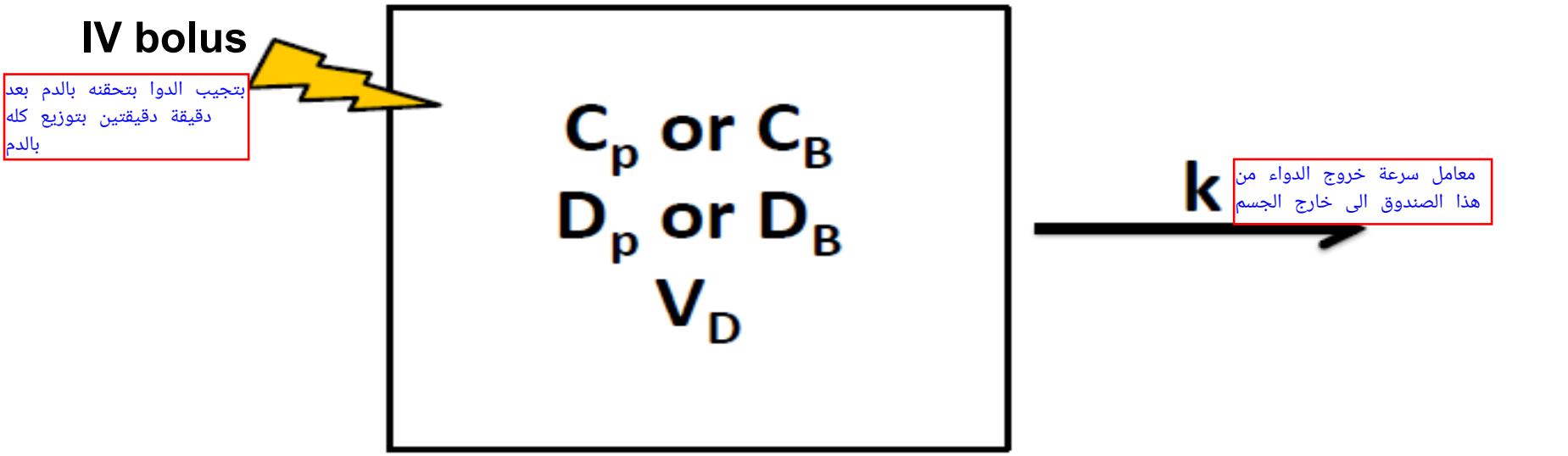
One compartment open model: intravenous bolus administration

PK theory lec.3

One-compartment model

- IV bolus- One compartment model:



Open compartmental model

Cont,

distribution , elemination
or
distribution , metabolism , excretion

- 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.

افترض انه الجسم عبارة عن بوكس واحد وتم حقن الدوا فيه وتوزع الدوا بشكل متساو في جميع انحاء الجسم

metabolism + excretion

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

برضو افترض انه الدوا ببلش يصيرله استقلاب وطرح من اول ما يدخل على الجسم يعني عند وقت يساوي صفر

One-compartment model assumptions

Assumptions

- Drug is mixed instantaneously (فوريًا) in blood or plasma.

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

- Drug elimination follows first order kinetics.

هون عنا ثلاث افتراضات تعتبرهم ك شروط لفرضية اعتبار كل الجسم ك بوكس واحد
اول شي نفرض انه عند حقن الدواء في الجسم يتوزع بنفس الثانية في كل نقطة في الدم بشكل متساوي
ثاني شي بنفترض انه بصير توازن سريع بين الدوا الموجود بالانسجة والدم يعني كمية الدوا الموجودة ثابتة والتغير بينهم فوري في الجهتين (من تركيز الدوا بالدم بنعرف تركيزه بالانسجة)
ثالث فرضية انه الدوا يتناقص بنسبة مئوية ثابتة

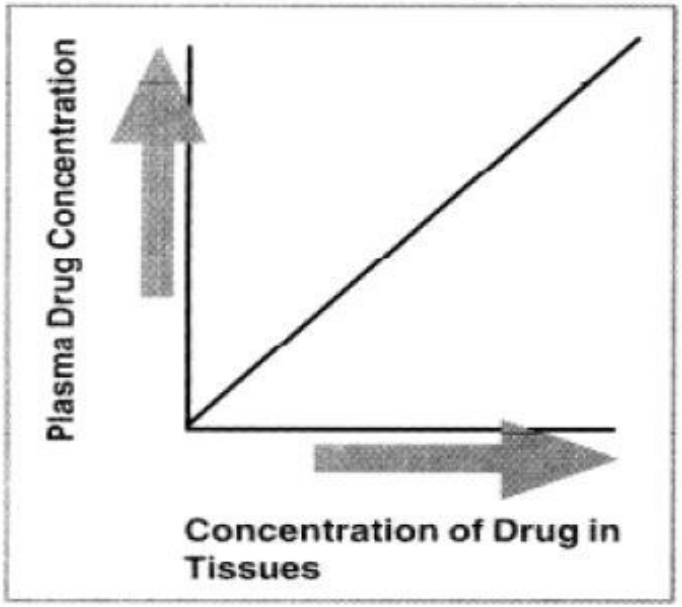


Figure 1.2. Relationship of plasma to tissue drug concentrations.

Cont,

Drug in the blood (plasma) is in rapid equilibrium with drug in the extravascular tissues what this statement means?

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

- 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. and vice versa.

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.

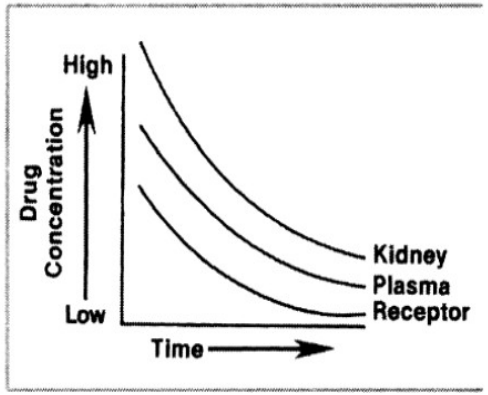


Figure 1.3. Drug concentration versus time.

Cont,

يعني اذا زادت كمية الدوا في الدم رح تزيد في اي نسيج ثاني

↓

الهم نفس الميل بس مش نفس الانترسيبت

proportional into another tissues

drug amount or concentration in blood equal to any tissue

- 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.

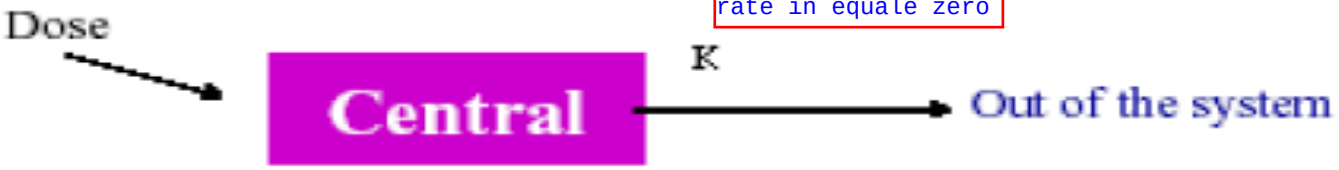
يعني لو نزل تركيز الدواء في الدم بنسبة ٢٠٪ لازم ينزل في الانسجة (المكان اللي فيه المرض) بنفس النسبة ٢٠٪ وفي نفس اللحظة

- 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.

Cont,

1-Comp. Model: IV Bolus Dosing

isn't present rate
rate in equale zero



Xt: the amount of drug remained in the compartment

K: first-order elimination rate constant (**OVERALL**)

(unit = time^{-1})

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

$\frac{1}{T} = \frac{X}{T}$

IV bolus:rate in zero rate out first
IV infusion:rate in zero order rate out first order
orally drug: rate in and rate out are first order

all route of administration the rate out are first order

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)

elimination= metabolism and excretion

$$k = k_e + k_m$$

k_e : 1st order rate constant of excretion

k_m : 1st order rate constant of metabolism

example :-

$K = 0.1\ hour^{-1}$, 60% elimination by liver (metabolism)

Calculate the K_e ?!

$K_m = 0.1 * \frac{60}{100} = 0.1 * 0.6 = 0.06$

$K_e = 0.1 * 0.4 = 0.04$

Cont,

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

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

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

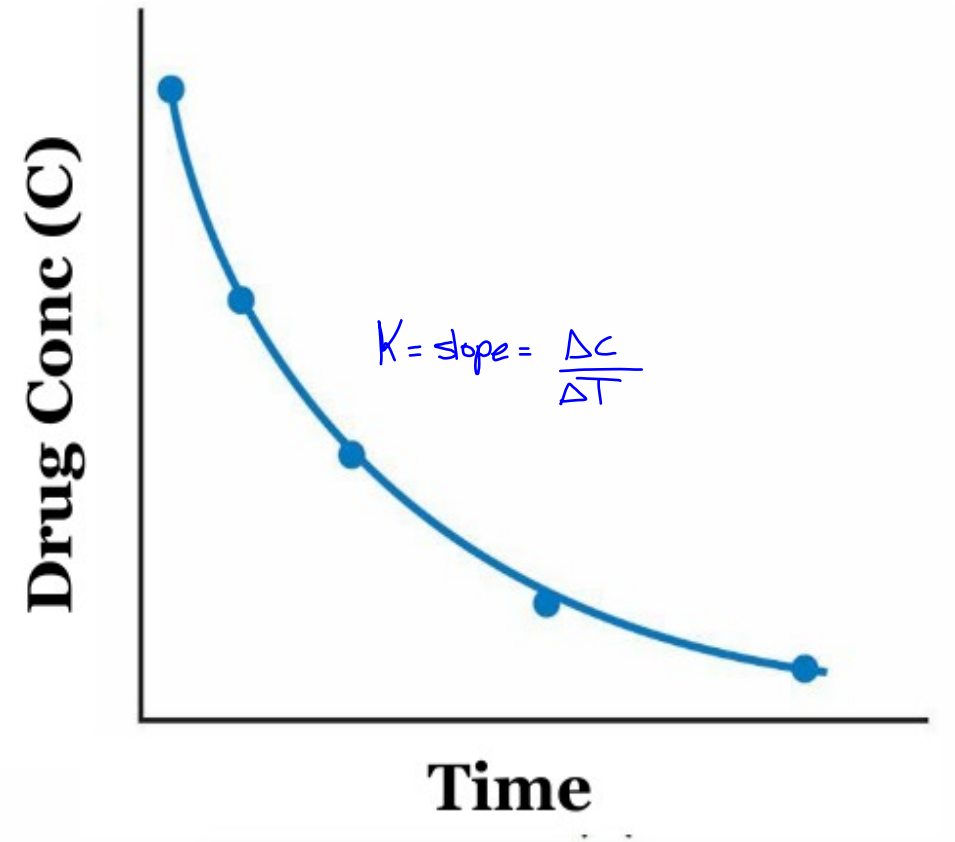
$$\log D_B = -\left(\frac{k}{2.303} \times t\right) + \log D_B^0 \ldots\ldots\ldots [log]$$

هون بتقدر نطلع الميل والانترسيبت

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

بتقدر تطلع الانترسيبت بس ما بتقدر تطلع الميل

One compartment open model



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

C= concentration

D= dose

Vd: Volume of distribution

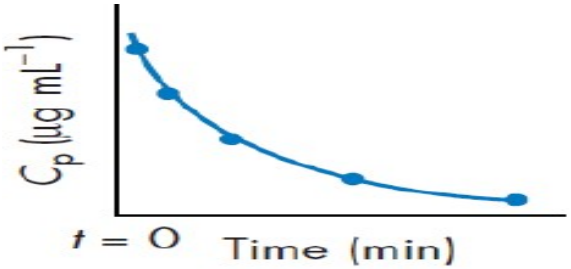
K: elimination rate constant

t: time

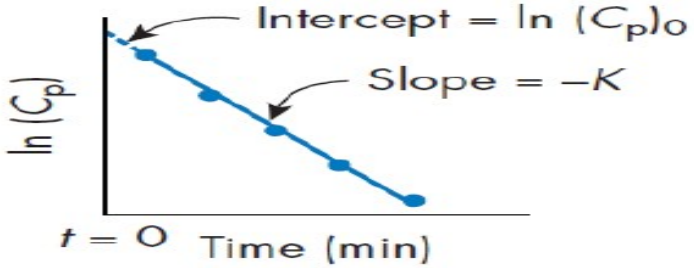
- As we usually take samples from the plasma or blood → then the results are in concentration units not mass units
- So we will have V_D and C_p →

وحدات التركيز مقابل وحدات الكتلة:
المختبر لما يسحب دم ما بيقدر يقولك جسم المريض فيه 500 ملجم دواء هو بيعطيك تركيز يعني بيقولك كل لتر دم فيه ١٠ ملجم انت كصيدلي لازم تحول هذا الرقم لـ كمية او كتلة عشان تعرف كم باقي دواء في جسم المريض
ليش بنحتاج نحسب الحجم اللي توزع فيه الدوا؟
تخيل هو المعامل اللي بيحول لك التركيز اللي شفته في عينة الدم الصغيرة لـ كمية دواء موزعة في الجسم كامل

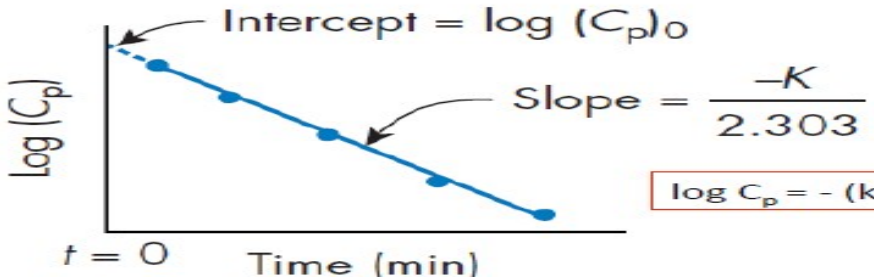
$$D_B = V_D * C_p$$



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

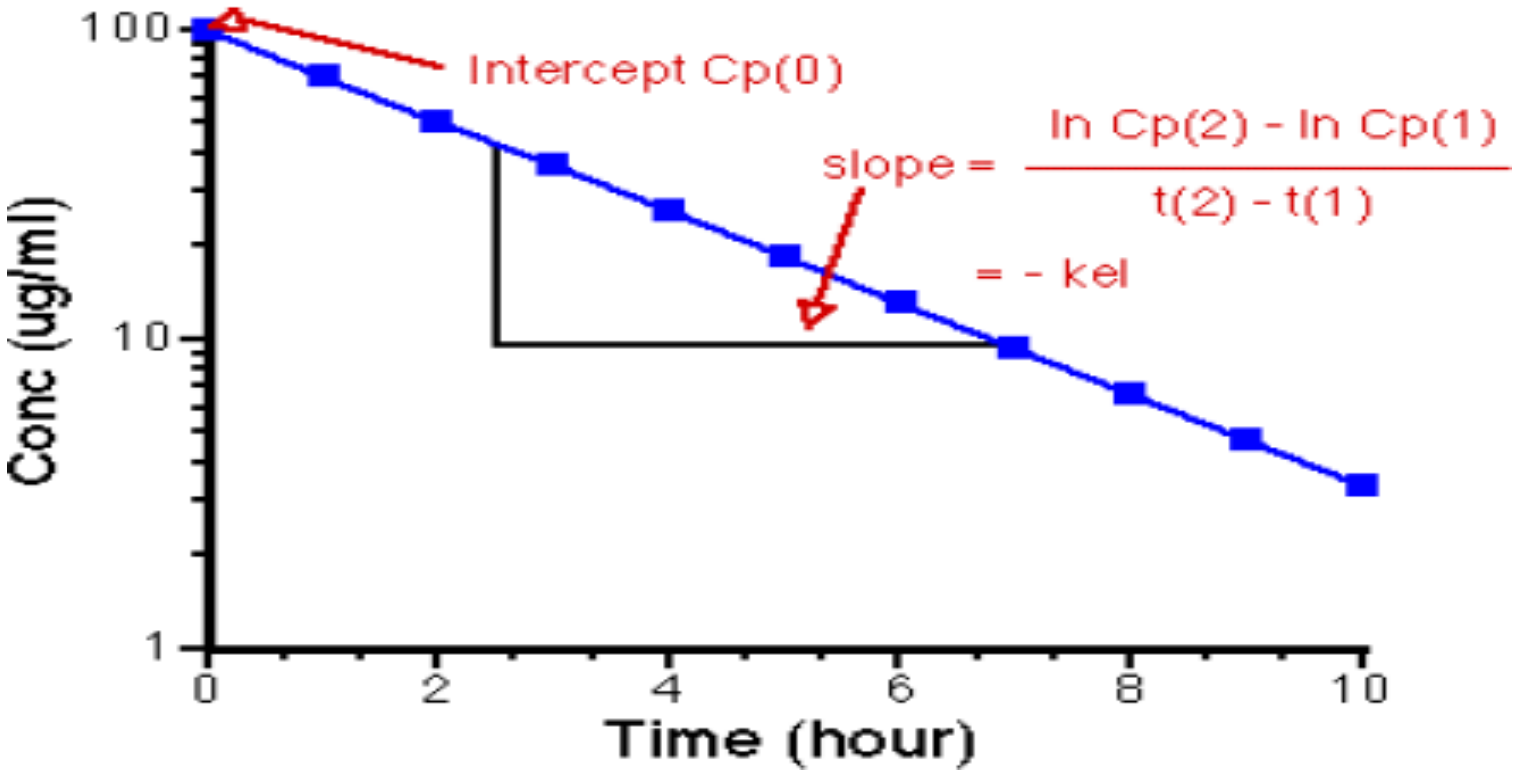


$\ln C_p = - k*t + \ln C_p{}^o$



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

Determination of K



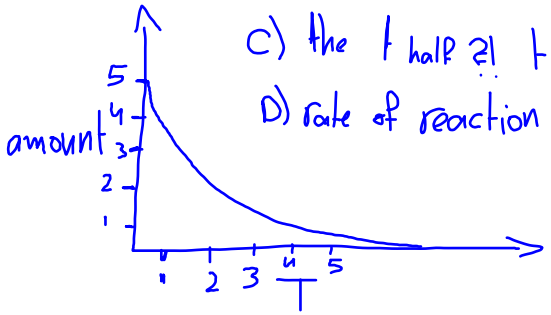
exampl
e

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

$\ln A = -Kt + \ln A^\circ = -(0.173)(2) + \ln 5$

$\ln A = 1.26 \Rightarrow A = 3.53$



C) the t half =? $t = 0.693/K = 0.693/0.173 = 4$ hr

D) rate of reaction after three hour?!

رح نلاحظ انه سرعة التفاعل رح تقل كل ما زاد الوقت

$\frac{dx}{dt} = -Kx = -0.173 * 3.53$

$= -0.6$ mg/hr

rate of reaction equal -0.6
rate of elimination equal 0.6

PK parameters

Fundamental parameters in one compartment

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

Apparent Volume of Distribution (Vd)

كل ما كان الدوا عنده قابلية يدخل على الانسج عالية بالتالي رح يزيد حجم التوزيع

- •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.

لا يمكن ان يكون حجم التوزيع اقل من حجم الدم ولكن ممكن ان يكون اكبر من حجم الدم

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

$$V_d = \frac{\text{AMOUNT of drug in the body}}{\text{CONCENTRATION in plasma}} = \frac{A_0}{C_0}$$

at $t = zero$

$t = zero$

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

حجم التوزيع : هو مقياس لميل الدواء للانتقال من بلازما الدم الى مواقع اخرى في الجسم

drug A $\Rightarrow A_0 = 100$, $C_0 = 10 \Rightarrow V_d = \frac{100}{10} = 10\,L$

drug B $\Rightarrow A_0 = 100mg$, $C_0 = 1$, $V_d = \frac{100}{1} = 100L$

drug C $\Rightarrow A_0 = 100\,mg$, $C_0 = 0.1$, $V_d = \frac{100}{0.1} = 1000L$

drug D $\Rightarrow A_0 = 100mg$, $C_0 = 0$, $V_d = \frac{100}{0} = \infty L$

عندي خيارين يا كذب ما انعطى دوا يا راح كل الدول للانسجة يعني بطل في دوا بالدم

volume of distribution is drug properties not physiological properties

كل ما قل التركيز رح يزيد حجم التوزيع

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:

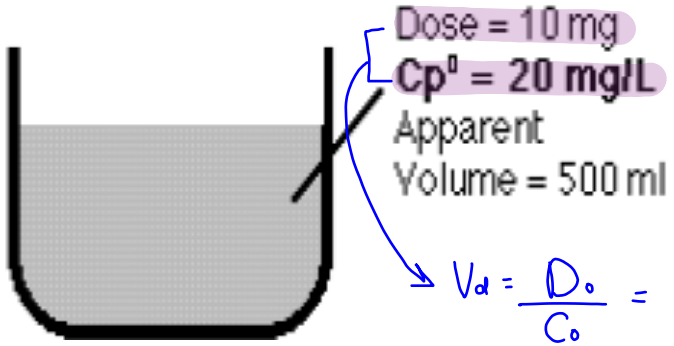
العوامل التي تؤثر على التوزيع هي نفسها العوامل التي تؤثر على الامتصاص

- **Rate of distribution**
- Membrane permeability — high penetration=>high volume of distribution — BBB hasn't pores the drug can penetrate it must be more lipophilic
- Lipid Solubility — high lipid solubility=> high affinity to penetrate the phospholipid bilayer=> high volume of distribution — لازم يكون جزء محب للماء وجزء كاره للماء
- pH - pKa (pH-partition theory for ionizable molecules) — unionized drug => more affinity to penetrate=> high volume of distribution
- Blood perfusion of organs and tissues — كل ما كان العضو او النسيج بوصله دم اكثر كل ما زاد التعرض للدوا بالتالي يزيد حجم التوزيع
- **Extent of Distribution**
- Plasma protein binding — increase protein binding=> decrease penetration=> decrease volume of distribution → in plasma, blood
- Intracellular binding — increase protein binding in tissue=> increase volume of distribution

Volume of distribution

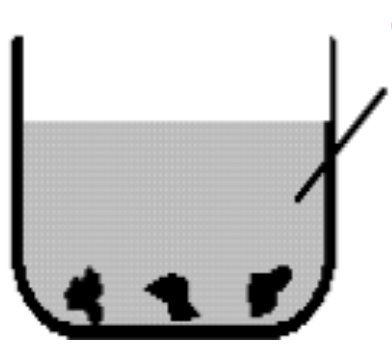
Definition: $V = \frac{\text{amount of drug in the body}}{\text{concentration measured in plasma}}$

Drug concentration in beaker:



$V_d = \frac{D_o}{C_o} = \frac{10}{20} = 0.5\,L \times \frac{1000\,mL}{L} = 500\,mL$

With charcoal in beaker:



$V_d = \frac{D_o}{C_o} = \frac{10}{2} = 5L$

$5L * \frac{1000\,mL}{L} = 5000\,mL$

هون بنلاحظ لما قللنا التركيز وبالجهتين كانت الجرعة ثابتة زاد حجم التوزيع يعني العلاقة بين حجم التوزيع والتركيز علاقة عكسية

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

العلاقة عكسية بين حجم التوزيع والتركيز

- **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

حجم التوزيع بدل عنا ع مدى توزع الدوا بالجسم فكلما كان حجم التوزيع عالي هذا يدل على انه عنده قابلية عالية يروح ويتوزع بالانسجة

Cont,

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

↑ drug distribution → ↑ V_D

e.g.

Plasma - 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

طلعنا هاي القيم عن طريق قسمة حجم التوزيع على وزن ٧٠ كغ

بحفظ انتاج خلايا الدم بكون بالكلية بس بنعطيه ك دوا احيانا

volume of distribution coefficient

حتى يطلعهم افترض انه وزن الشخص ٧٠كغ

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*

* Distribution Coefficient

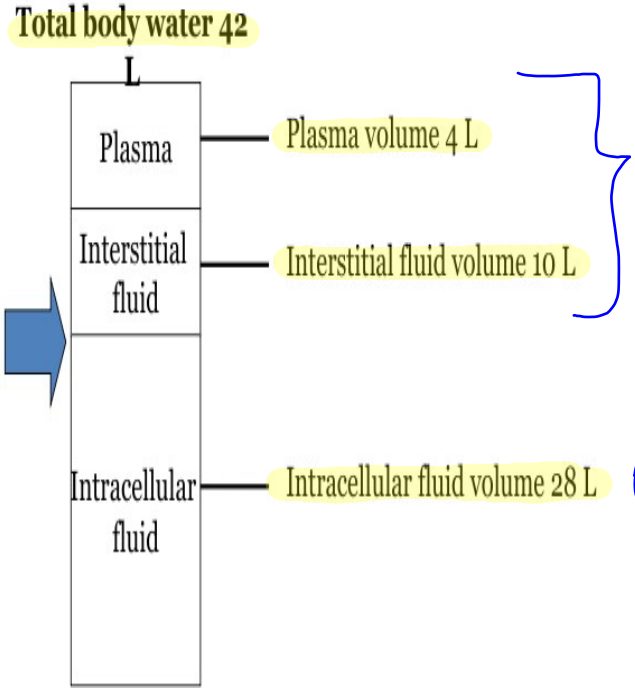
antimalarial drug
have low molecular weight, unionized, high lipophilic, highly tissue protein binding

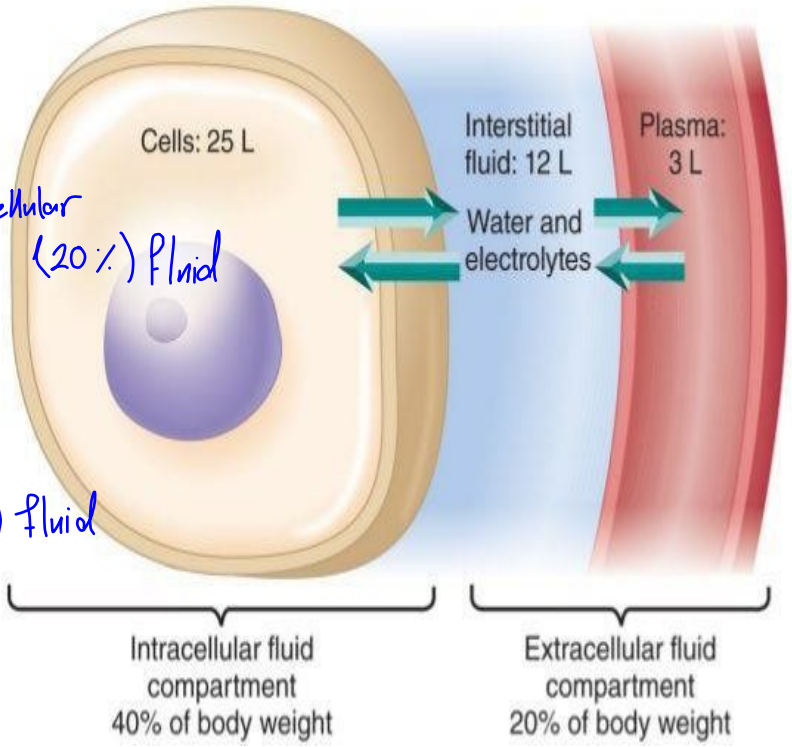
* distribution coefficient was 1 L/Kg and the weight of person equal 70 Kg what the volume of distribution ?!

volume of distribution = distribution coeffient * weight = 1 L/Kg * 70 Kg = 70 L

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

جسم الانسان فيه ٦٠٪ سوائل وكغ ٧٠





مثلا لو حجم التوزيع يساوي اربعة يعني الدوا توزع بس بالبلازما
لو كان مثلا عشرة معناها توزع كامل بالبلازما وراح لجزء من السائل بين الخلايا
واذا كان مثلا ١٤ يعني غطى حجم السائل بين الخلايا والبلازما
ولو كان اكثر يعني راح للسائل داخل الخلايا

higher volume of distribution=∞
lower volume of distribution=3-4

اذا بدي ياه يروح للسائل داخل الخلايا لازم اعمل الدوا
Lipophilic with low hydrophilicity , unionized, low molecular weight
حتى يمر من خلال الغشاء ويروح للسائل داخل الخلايا

مثلا دوا مضاد للتخثر زي الوارفارين بدي ياه يظل بالدم عشان هيك بعمله
ionized, hydrophilic, high molecular weight (Heparin), highly plasma proteins binding

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)

هالدواء بتوزع في البلازما والسائل بين الخلايا

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.

ينتشر عبر البلازما و السائل بين الخلايا والسائل داخل الخلايا

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

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

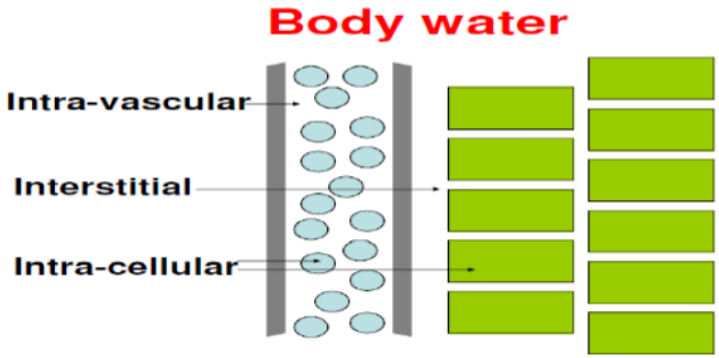
رح يغطي حجم البلازما والسائل الخلالي ويروح يغطي جزء من السائل بين الخلايا

اذا كان اقل من واحد رح يفرق معنا ونحتاج نضربه بالوزن حتى نعرف حجم التوزيع

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.

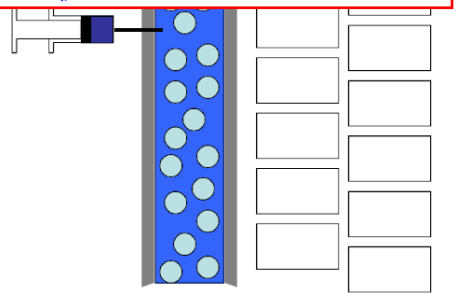
بس هون بيرجع يحكي انه اقل قيمة لحجم التوزيع من ٣ل٤ ومستحيل تكون اقل بس ما في حد لاعلى قيمة يعني ممكن تكون لا نهاية والمثال موجود بالسلايد ١٥



Distribution - Evan's Blue

Intra-vascular space only

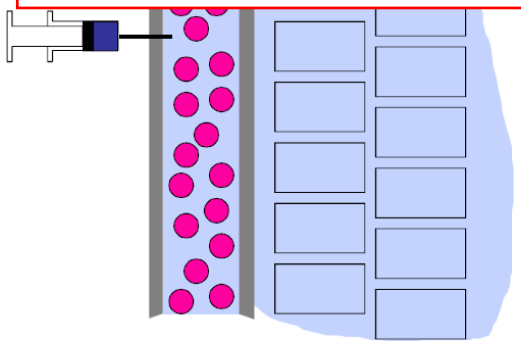
المساحة داخل الاوعية الدموية فقط يعني التوزيع بس بالبلازما



Distribution - Aminoglycosides

All water

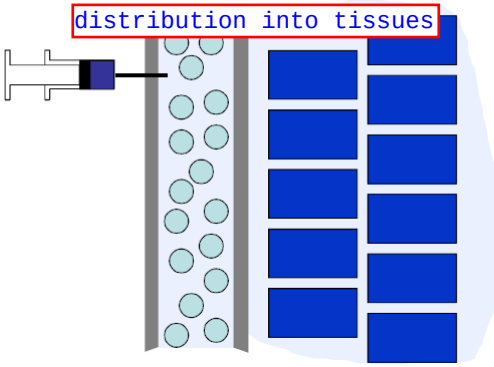
distribution in extracellular fluids



Distribution - Quinacrine

Concentration into cells

distribution into tissues



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_o)
4. Estimate Vd:

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

Extracting AUC

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

amount = V * concentration

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

rate = -K C_0 V_d

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

$$dD_B = -kV_D C_p dt$$

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

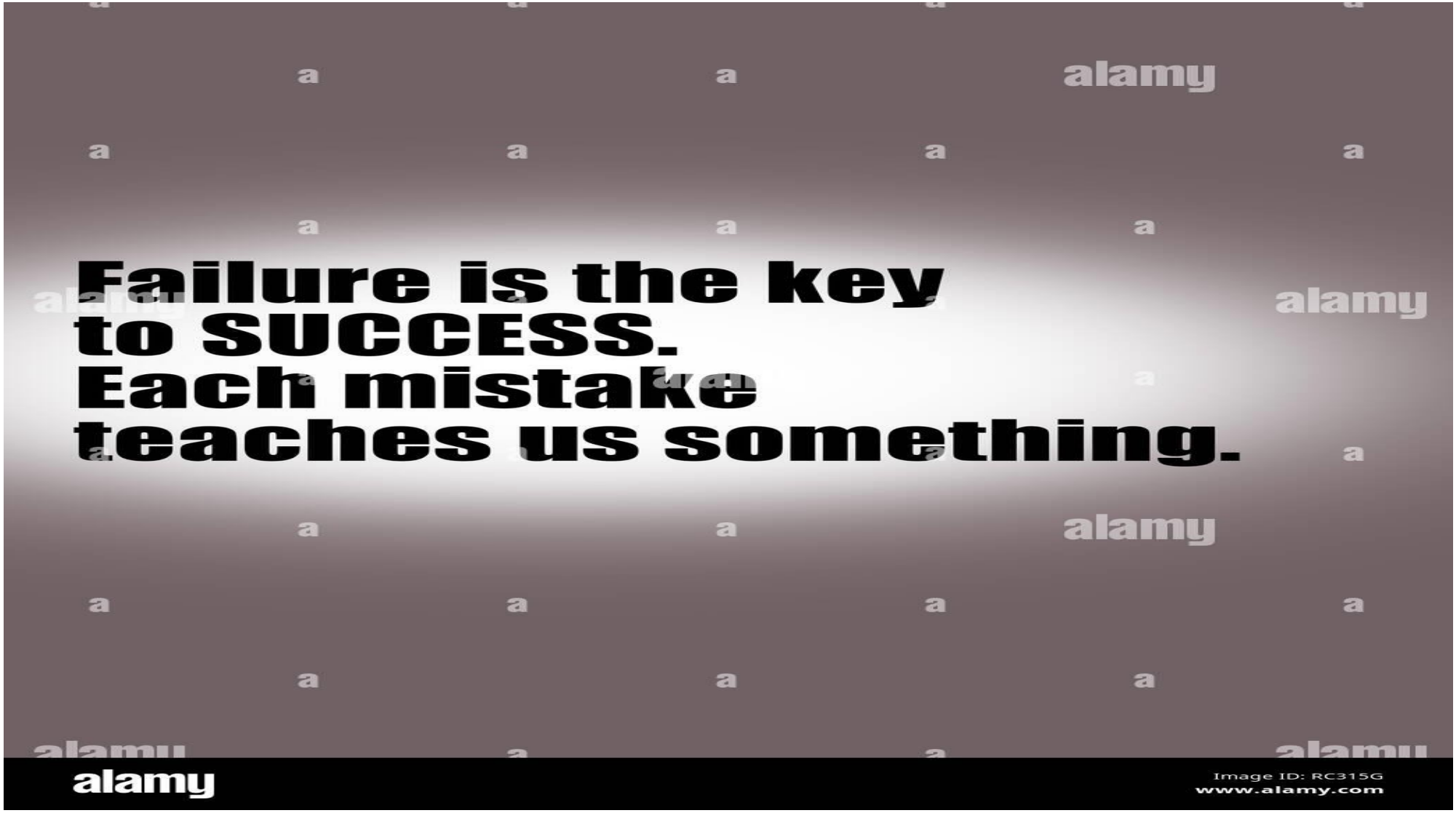
Volume of distribution vs AUC

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

$$D_0 = kV_D[\text{AUC}]_0^\infty \Rightarrow [\text{AUC}]_0^\infty = \frac{D_0}{kV_D} = \frac{C_0}{k}$$

which upon rearrangement yields the following equation:

$$V_D = \frac{D_0}{k[\text{AUC}]_0^\infty} \qquad (4.13)$$




The End.