PK models and basic PK calculations

PK theory material lecture.2

Importance of PK

*Knowledge of the pharmacokinetic behavior of drugs in animals and human is crucial in drug development, both to make sense of preclinical toxicological and pharmacological data and to decide on an appropriate dose and dosing regimen for clinical trials.

*Drug regulators have developed concepts such as **bioavailability** and **bioequivalence** to support the licensing of generic versions of drugs produced when originator products lose patent protection.

عندما تفقد المنتجات الاصلية حماية براءة الاختراع مدتها خمس سنوات

Basic Pharmacokinetics and Pharmacokinetic model

- Drugs are in a dynamic state within the body as they move between tissues and fluids, bind with plasma or cellular components, or are metabolized. The biologic nature of drug distribution and disposition is complex, and drug events often happen simultaneously.

- Such factors must be considered when designing drug therapy regimens. The inherent and infinite complexity of these events requires the use of mathematical models and statistics to estimate drug dosing and to predict the time course of drug efficacy for a given dose.

PK models

- Model: a hypothesis using mathematical terms to describe quantitative relationships concisely.

فرضية بتستخدم معادلات رياضية لحل شي
بيسحب واله كمية

- Pharmacokinetic parameter: is a constant for the drug that is estimated from the experimental data.

fundamental pharmacokinetics parameters:
k: elimination rate constant
d: volume of distribution
t: half time
clearances:
معدل خروج الدواء من الجسم

Basic pharmacokinetics and pharmacokinetic model

- A pharmacokinetic function relates an independent variable to a dependent variable, often through the use of parameters.

- For example, a pharmacokinetic model may predict the drug concentration in the liver 1 hour after an oral administration of a 20-mg dose. The independent variable is the time and the dependent variable is the drug concentration in the liver. Based on a set of time-versus-drug concentration data, a model equation is derived to predict the liver drug concentration with respect to time.

- Such mathematical models can be used to describe and predict drug concentrations in the body as a function of time

يمكن استخدام هذه النماذج الرياضية لوصف والتنبؤ
بتركيزات الدواء في الجسم كدالة في الزمن

Graphs

concentration or amount

بنحط
amount
بدل التركيز اذا كان
volume of
distribution
ثابت

Dependent variable

Independent variable

time

تخيل الجسم كانه وعاء وفيه سائل وهو الدم
لما نحط صبغة وهي الدواء في هذا الوعاء
لو الصبغة ظلت ذائبة في السائل بس بيكون تركيزها عالي بالسائل وهذا يعني ان حجم التوزيع
صغير لانها محبوسة بالدم
لو الوعاء فيه اسفنج مثل الدهون او العضلات والصبغة هذي تحب تمسك بالاسفنج بتلاحظ ان
اغلب الصبغة تركت السائل وراحت للاسفنج وقتها لما تقيس تركيز الصبغة بالسائل بتلاقيه قليل
جدا وهذا يعني ان حجم التوزيع كبير لانها توزعت في كل مكان بعيد عن الدم
الخلاصة
كل ما الدواء هرب من الدم وراح للاسفنج وهي الانسجة كل ما زاد رقم حجم التوزيع
وكمان اذا تخيلنا الموضوع ك وعاء مثقوب بالشخص الكبير او المريض هذا يعني انه السائل قل
ورح يقل توزع الدواء بالسائل ويروح للانسجة والشخص السليم بوعاء سليم حجم التوزيع تبعه
ثابت

Compartmental PK

نتخيل الجسم على شكل بوكسات

غير محدود — نبنيه

- Theoretically, an unlimited number of models may be constructed to describe the kinetic processes of drug absorption, distribution, and elimination in the body, depending on the degree of detailed information considered.

- A very simple and useful tool in pharmacokinetics is **compartmentally based models**. النماذج القائمة على الحجرات

- It is common and useful practice to divide objects of scientific interest into smaller conceptual units until the underlying mechanisms become apparent.

من الممارسات الشائعة والمفيدة تقسيم المواضيع العلمية الى وحدات مفاهيمية اصغر حتى تصبح الآليات الاساسية واضحة

يعني مثلا نقسم الجسم لبوكسين او اكثر مثل نحط انه الدوا بوصل اكثر شي
للدم والكبد [redacted] والكلى وبالبوكس الثاني نحط الجلد والدهون والعضلات

PK models

- Compartmental models are used, and they are simplified models in which the body is conceived to be composed of mathematically interconnected compartments (depicted as boxes)
- **Compartmental model are two types:**

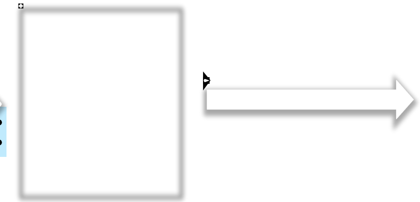
  A. Empirically-based conventional models

  B. Physiologically-based pharmacokinetic (PBPK) models

النماذج التقليدية هذي بنعتبر فيها الجسم غرفة واحدة او غرفتين بس
عشان نسهل الحسابات الرياضية وما بنهتم فيها بشكل العضو الحقيقي
نماذج بي بي بي كي هذي اكثر دقة لاننا بنرسم كل عضو مثل الكبد
او الكلية كصندوق لحاله وبنحسب سرعة تدفق الدم لكل عضو وتركيز
الدواء فيه بالتفصيل

Compartmentally-based model

* Simple
* The [drug] in the compartment for a given dose is determined by :



(1) The fluid volume (V) of the comp. اذا كان كبير تركيز قليل واذا كان صغير تركيز عالي

(2) The elimination rate of drug per unit of time. اذا زادت يعني تركيز اقل واذا قلت يعني تركيز اعلى

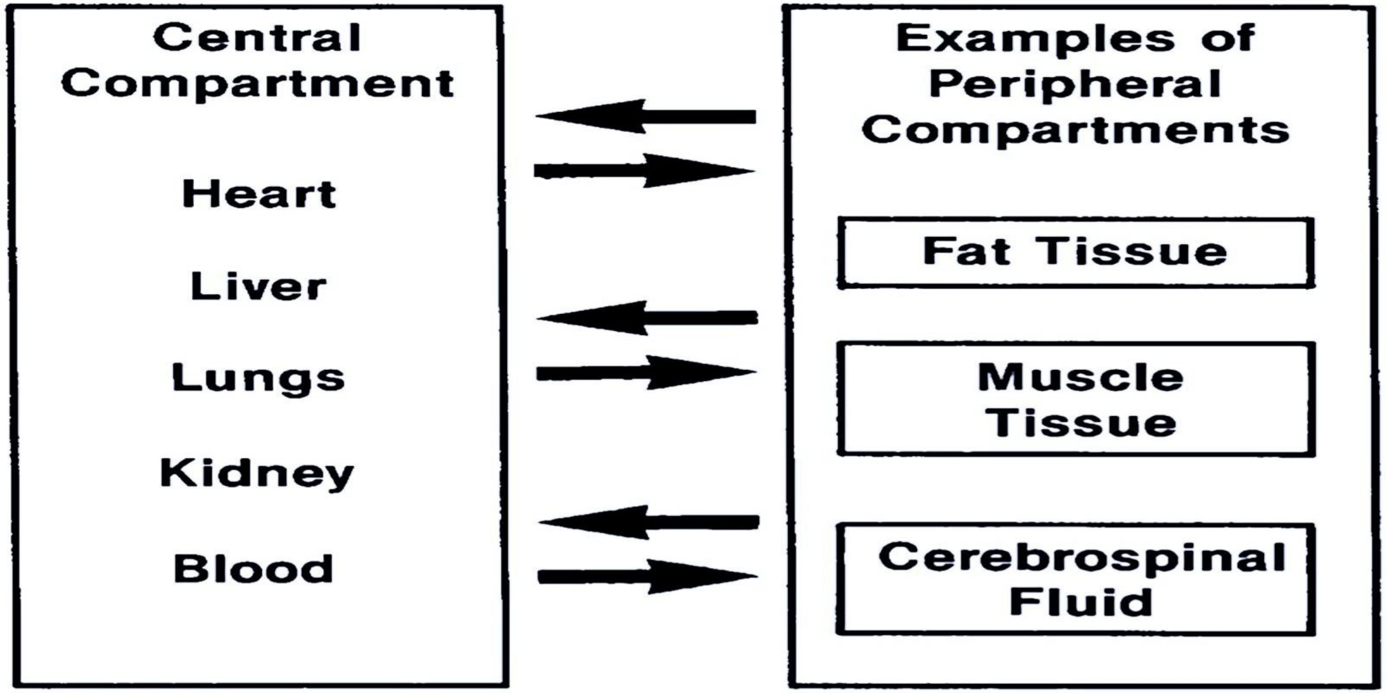
* One-compartment, two-compartment, or multi- compartment model.

* The compartments do not represent a specific tissue or fluid but may represent a group of similar tissues or fluids

لو عندنا اعضاء بيوصل لها الدم بسرعة كبيرة مثل القلب والرئة والكبد بنجمعهم مع بعض في صندوق ونسميه الحجرة المركزية
لو عندنا اعضاء بيوصل لها الدم ببطء مثل الدهون او العظام بنجمعهم في صندوق ثاني ونسميه الحجرة المحيطية

Cont

- Organs and tissues in which drug distribution is similar are grouped into one compartment.



Cont,

- Most PK models assume
- instant homogeneous distribution of drug within each compartment "well-stirred" نحط ببالنا انه كل بوكس فيه مجموعة وتوزع فيها الدوا بشكل متساوي بنسمي هالشي تحريك جيد
- and elimination rate constant does not change over time k قيمة ثابتة للدوا بتتغير في حالة كان الشخص عنده مشاكل بالكبد والكلى لانه ثابت معدل الإزالة يقل بارتفاع عمر النصف للدوا لانه اذا كان في مشاكل بالكبد والكلى رح يزيد عمر النصف للدوا
- Model parameters (e.g. V and k) are determined experimentally from a set of drug concentrations collected over various times لهدول بنعتبرهم ثابتين لكل دوا
- □ parameters □□complexity of the model
- □□ data needed
- Compartmental PK models are useful esp. when little information is known about the tissues

Mathematical review

- <u>Do you know?/ Can you?</u>
- The units used usually for concentration? molarity,mass\volume, molality, normality, percentage,part per million.....
- Calculate the amount of the drug in a solution with a known drug concentration and solution volume? In different volumes? amount=volume*concentration
- **<u>How to convert units?</u>**
- e.g. mg/mL to g/L and µg/µL.
- Calculate the MW of the drug?
- Units of concentration in M?

$$\frac{mg}{mL} \times \frac{1g}{1000mg} \times \frac{1000\,mL}{1\,L} = \frac{1g}{1L} = g/L$$

$$\frac{mg}{mL} \times \frac{1000\,\mu g}{1\,mg} \times \frac{1\,mL}{1000\,\mu L} = \frac{\mu g}{\mu L}$$

عدد الذرات * الوزن الذري لكل ذرة

$$mole = \frac{mass}{Mm} \Rightarrow Mm = \frac{mass}{mole}$$

cont

- If a known amount of drug was added and resulted in 0.6 mg/L (for example) concentration of the solution, what volume of water was in the container? according to the amount

- For the following equation: (y=1.8x+2)

a. **Sketch** a plot of the equation.

b. If $x = 0.5$, what is y? Y = 2.9 $y = 1.8 * 0.5 + 2 = 0.9 + 2 = 2.9$

c. If $y = 4.6$, what is x? X = 1.44 $4.6 - 2 = 1.8x \Rightarrow x = \frac{2.6}{1.8} = 1.44$

cont

- What is the slope of the line that connects the following two points? Slope= $\frac{\Delta y}{\Delta x} = \frac{8.6-4.5}{5-0.6} = \frac{4.1}{4.4} = 0.932$
- 1) x=5, y=8.6
- 2) X=0.6, y=4.5

SLOPE = 0.93

- Solve the following equations for *x*:
- a. log x = 0.95 — X = 8.9125 — $10^{0.95} = 8.9$
- b. e x = 0.44 — X = - 0.82098 — $x \ln e = \ln 0.44 \Rightarrow x = \ln 0.44 = -0.823$
- c. ln x = 1.22 (e, e) — X = 3.387 — $x = e^{1.22} = 3.39$

Basic exponent laws

- Expression: N

Laws of Exponents	Example
$a^x \cdot a^y = a^{x+y}$	$10^2 \cdot 10^3 = 10^5$
$(a^x)^y = a^{xy}$	$(10^2)^3 = 10^6$
$\frac{a^x}{a^y} = a^{x-y}$	$\frac{10^2}{10^4} = 10^{-2}$
$\frac{1}{a^x} = a^{-x}$	$\frac{1}{10^2} = 10^{-2}$
$\sqrt[y]{a} = a^{1/y}$	$\sqrt[3]{a} = a^{1/3}$

Logarithms

- If N=bx, then logb N= x $\Rightarrow \log_b N = x \Rightarrow b^x = N$
- Common logarithms (log)= logarithms using base 10
- Natural logarithms (ln) use the base *e*

e ≈2.718

2.303 log N= ln N

- A logarithm does not have units = dimensionless

Laws of Logarithms

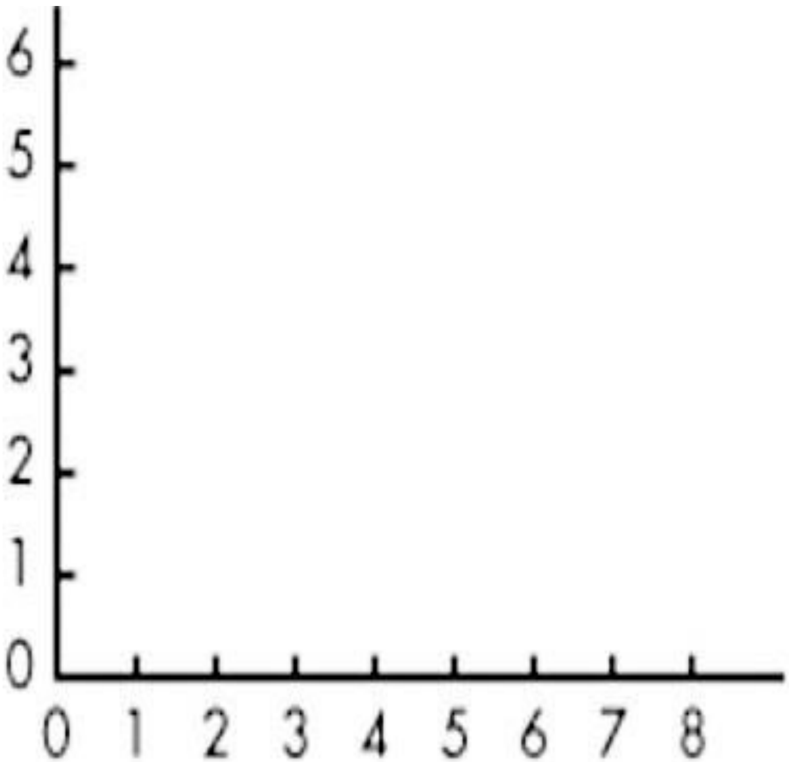
$$\log ab = \log a + \log b$$

$$\log \frac{a}{b} = \log a - \log b$$

$$\log a^x = x \log a$$

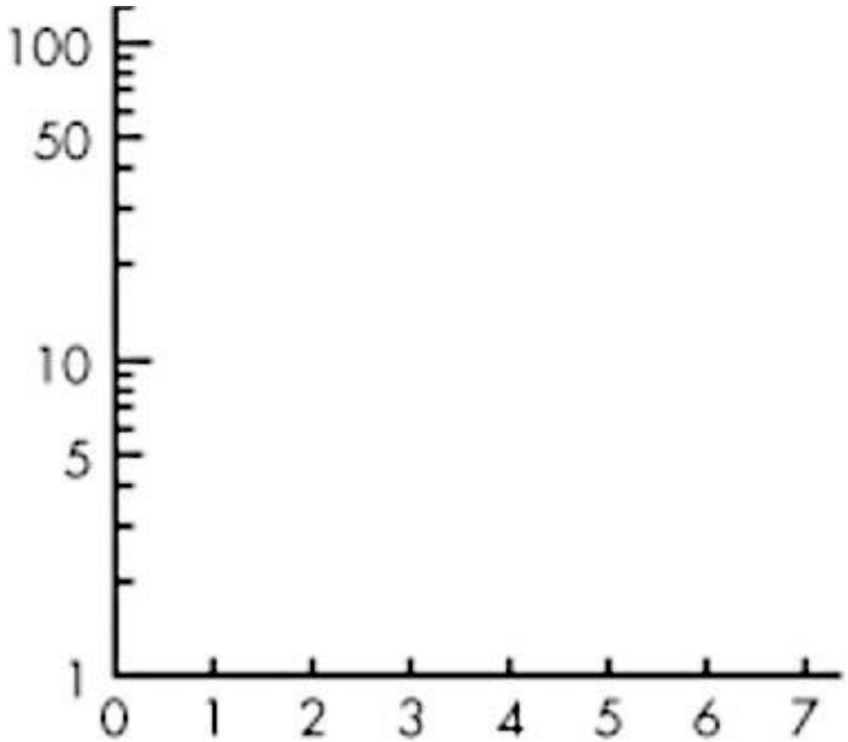
$$-\log \frac{a}{b} = +\log \frac{b}{a}$$

- Your calculator log, ln, anti-log and anti-ln



Rectangular coordinate graph

x and y
موزعين بشكل ثابت



Semilog coordinate graph

x
موزع بشكل ثابت
y
بينهم مسافات غير ثابتة

cont

- Straight line eqt.
- $$y = a x + b$$
- Slope? intercept? A B
- For a given straight line □ calculate slope (on rectangular or semilog graph)
- **<u>REMEMBER:</u>**

In semilog graphs : the y values are plotted on a logarithmic scale **without** performing actual logarithmic conversions, whereas the corresponding x values are plotted on a linear scale

ما بتقدر نطلع من ميلان
الميل بس بتقدر نطلع
انترسيبت لو بدنا نطلع ميل
بنحوله لخط مستقيم

في الرسم البياني نصف اللوغاريتمي يتم رسم قيم
المحور الصادي على مقياس لوغاريتمي بدون اجراء
تحويلات لوغاريتمية فعلية بينما يتم رسم قيم المحور
السيني المقابلة لها على مقياس خطي عادي

PK units

PARAMETER	SYMBOL	UNIT	EXAMPLE
Rate	$\frac{dD}{dt}$	$\frac{\text{Mass}}{\text{Time}}$ or $\frac{\text{concentration}}{\text{time}}$	mg/hr
(نفس الوحدة)	$\frac{dC}{dt}$	$\frac{\text{Concentration}}{\text{Time}}$	μg/mL hr $= \mu g\, mL^{-1} hr^{-1}$
Zero-order rate constant	k_0	$\frac{\text{Concentration}}{\text{Time}}$	μg/mL hr
		$\frac{\text{Mass}}{\text{Time}}$	mg/hr
First-order rate constant	k	$\frac{1}{\text{Time}}$ (day, week, month, year)	1/hr or hr^{-1}
Drug dose	D_0	Mass	mg
Concentration	C	$\frac{\text{Mass}}{\text{Volume}}$	μg/mL
Plasma drug concentration	C_p	$\frac{\text{Drug}}{\text{Volume}}$	μg/mL
Volume	V	Volume	mL or L
Area under the curve	AUC	Concentration × time	μg hr/mL
Fraction of drug absorbed (ليس لها وحدة)	F	No units	0 to 1
Clearance	Cl	$\frac{\text{Volume}}{\text{Time}}$	mL/hr $= mL\, hr^{-1}$
Half-life	$t_{1/2}$	Time	hr

→ mg/L × hr = $mg L^{-1} hr$

Rates and Orders of Reactions

- The rate of a chemical reaction of process is the velocity with which the reaction occurs. Consider the following chemical reaction:

Drug A ⟹ Drug B (metabolite)

- If the amount of drug A is decreasing with respect to time (that is, the reaction is going in a forward direction), then the rate of this reaction can be expressed as:

drug A
يتناقص عشان هيك بنحط سالب

- dA/dt → rate = mass / T , concentration / T

- Since the amount of drug B is increasing with respect to time, the rate of the reaction can also be expressed as:

تتزايد عشان هيك بنحط اشارة موجبة

+ dB/dt

- The rate of a reaction is determined experimentally by measuring the disappearance of drug A at given time intervals.

الكمية تبع الدوا بالزيرو ما يهمنا بتهمنا بالفيرست

Zero order reaction

- **Rate constants and order of Rx**
- Order of the Rx is the way that the [drug] affects the rate of the reaction or process ⇨
- Zero-order reactions or first-order reactions

$$- dA/dt = k*A^n$$

n □ determine the rate of the reaction

* Zero order reaction

!مقدار التناقص للدوا مع الوقت ثابت يعني لو اعطينا دوا ١٠٠ملغ.. بعد ساعة صار ٩٥ بعد ساعتين صار ٩٠ بعد ثلاث ساعات بصير؟ ٨٥

0.001 from drug

- Drug A is decreasing at a constant time interval t

n =0

(5mg/h) لـ التناقص

التناقص تبعه (as amount)

$$dA/dt = -k_0*A^0$$

$$dA/dt = -k_0$$

تعني تناقص وليس اشارة قيمة

direction

k0: is the zero-order rate constant Unit of k0 : **mass/time** (e.g. g/h)

or concentration/time

unit the same unit for rate

$mg \cdot mL^{-1} \cdot hr^{-1}$

$dA/dt = - k_0$

□ Rearrange

□ Integrate

$$A = - k_0 \, t + A^{\circ}$$

~~A0~~

↳ slope ↳ intercept

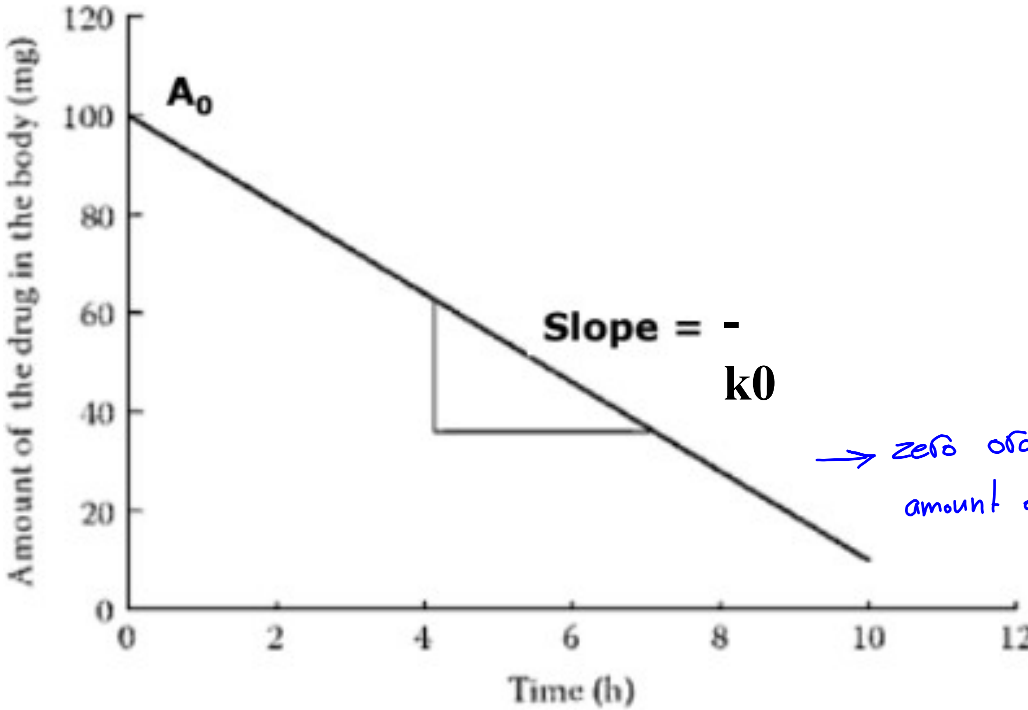
A: amount at any time

k_0: zero order rate constant

A_0 initial amount

:

$$A = -k_0 t + A_0$$



Slope = - k0

→ zero order is linear relationship
amount of decreasing is constant

Concentration □ $C = -k_0 t + C_0$

Half-life(t1/2)- Zero order

example: ethanol

اذا غيرنا الجرعة رح يختلف الزمن

- The period of time required for the amount (A) or concentration (C) of a drug to decrease by one- half.

- Zero-order half-life:

$T_{1/2}$ علاقتها طردية مع

$$t_{1/2} = (0.5\ A_0)\ /\ k_0$$

$A = -Kt + A_0$

$0.5A_0 = -Kt + A_0$

$+0.5A_0 = +Kt \Rightarrow t = 0.5A_0/K$

- The zero-order **t1/2** is proportional to the initial amount or concentration of the drug (**A0**) and is inversely proportional to the zero-order rate constant (**k0**).

في علاقة طردية بين التركيز الأولي وعمر النصف هذا الإشي بدل على إنه عمر النصف مش قيمة ثابتة بزيد لأودر

- **The time required for the amount to decrease by one-half is NOT constant**

عمر النصف في zero order ليس قيمة ثابتة

the properties of zero order reaction?
amount of decrease constant
rate of elimination constant
t1/2 not constant

Zero-Order Reactions: example

dose /amount A_0

- The administration of a 1000 mg of drug X resulted in the following concentrations:

بدنا ننتبه على التركيز والوقت حتى نحدد نوع الاوردر سواء فيرست او زيرو

what is the volume of distribution ?!

$$\text{concentration} = \frac{\text{mass}}{\text{volume}} \Rightarrow \text{volume} = \frac{\text{mass}}{\text{concentration}} = \frac{1000}{100} = 10\,L$$

عكس نطلع عن المنحنى مكان

Time x	Conc. (mg/L) y
0	100 → intercept
4	−10 90
6	−5 85
10	−10 75
12	−5 70

rate constant can be calculated in this example by $\Rightarrow \frac{\Delta y}{\Delta x}$

$$\frac{100-90}{0-4} = \frac{-10}{4} = -2.5\ mg/L\,hr$$

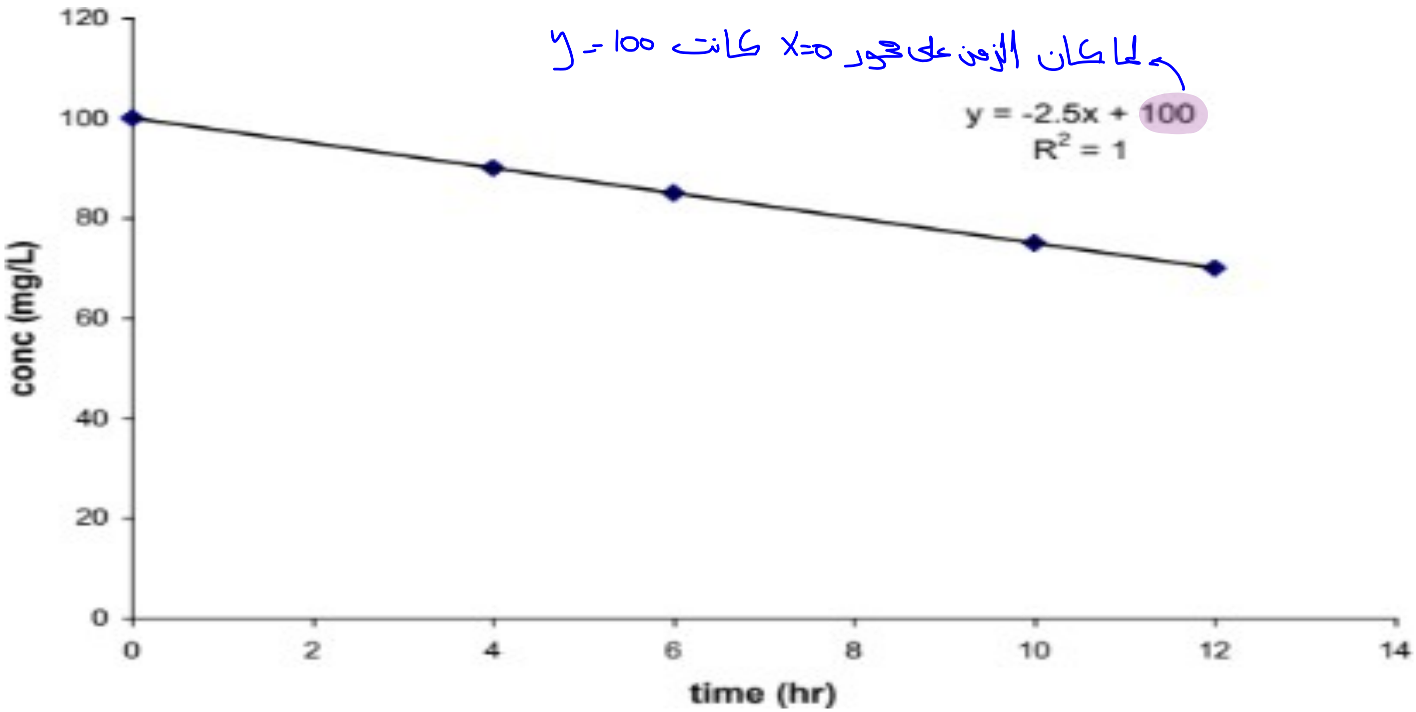
Zero-Order Reactions: example

- What is the order of the elimination process (zero or first)?

- What is the rate constant?

Constant = slope = $\frac{\Delta y}{\Delta x} = \frac{90 - 100}{4 - 0} = -2.5$ mg/L hr

Zero-Order Reactions: example



Zero-Order Reactions: example

- Since the decline in drug conc. displayed a linear decline on normal scale, drug X has a zero order decline.

- From the equation displayed on the figure (intercept = 100, slope = -2.5)

- The elimination rate constant is 2.5 mg/hr the rate is constant as percentage

First order reaction

→ التناقص تبعه بكون as percentage.

عنا دوا ١٠٠مغ.. يتناقص بنسبة
١٠٪ بعد ساعة رح يصير ٩٠مغ
بعد ساعتين رح يصير 81

9.999% from drug

كل دراستنا بتعتمد على هاد النوع

- If the amount of drug A is decreasing at a rate that is proportional to A, the amount of drug A remaining in the body, then the rate of elimination of drug A can be described as:

$dA/dt = -K_0$
$dA/dt = -K * A_1$

$$dA/dt = -k^*A_1$$

elimination rate constant is constant while elimination rate for first order is not constant because the rate depend on amount

لمجاب بالامتحان

الفرق بينهم هي وجود A
التي تمثل الكمية وهذا يعني ان الزيرو لا يعتمد على الكمية بينما الفيرست يعتمد على الكمية اللي ظلت

while in zero order the elimination rate is constant

- k: is the 1st order rate constant

- The reaction proceeds at a rate that is dependent on the concentration of A present in the body.
- A first-order reaction is a reaction that proceeds at a rate that depends linearly on only one reactant concentration.
- It is assumed that the processes of ADME follow first-order reactions and **most drugs** are eliminated in this manner

First order reaction

- The amount of a drug with first order elimination is described according to the following equation:

$$A = A_0 e^{-k^* \cdot t}$$

$$\ln A = \ln A_0 e^{-k^* \cdot t} \Rightarrow \ln A = \ln A_0 + \ln e^{-Kt} \Rightarrow \ln A = \ln A_0 - Kt$$

where A is the amount of drug in the body, A_0 is the amount of the drug at time zero (equal to the dose in the case of IV bolus)

- This equation is equivalent to:

$$\ln(A) = \ln(A_0) - k^* \cdot t$$

- **dA/dt= - k*A**

- A= A0*e(-kt)…………………. [e]

- ln A = - k*t +ln A0………………… [ln]

$$\frac{2.303 \log A}{2.303} = -\frac{Kt}{2.303} + \frac{2.303 \log A_0}{2.303} \Rightarrow \log A = -\frac{Kt}{2.303} + \log A_0$$

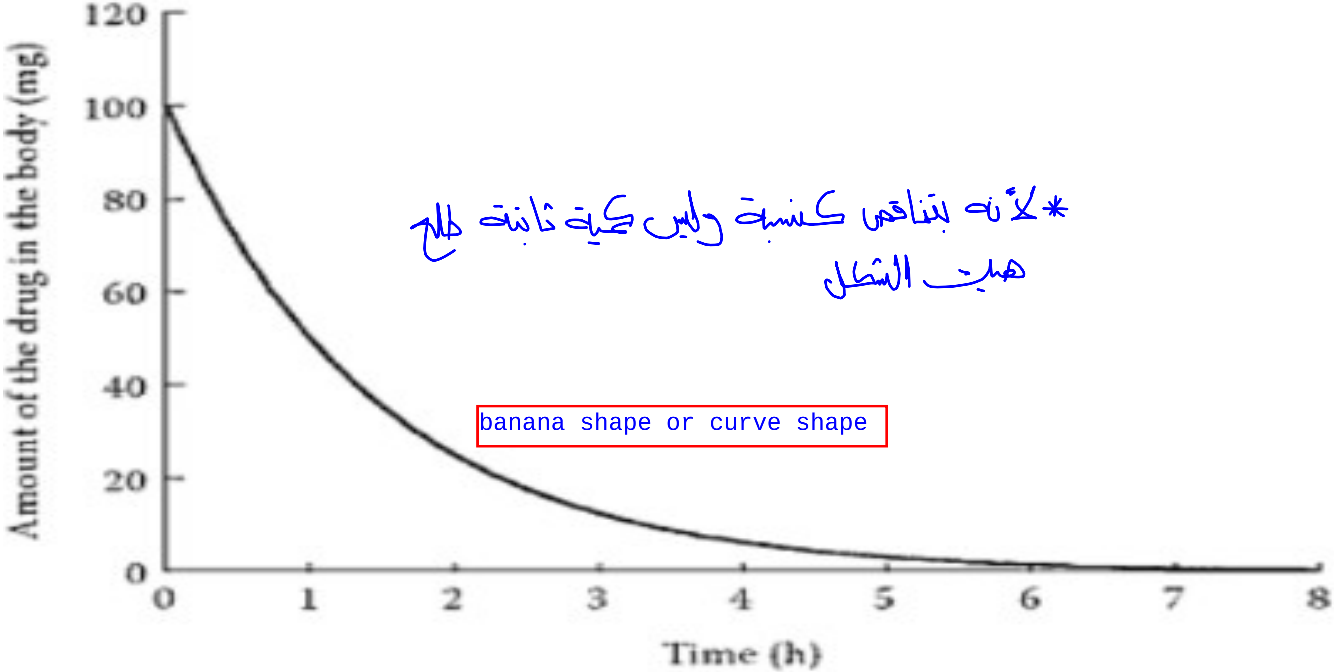
- log A = - (k*t/2.303)+ log A0……......... [log]

متساوين

$K = \frac{1}{time}$

- **A, k, A0:**

Drug with first order kinetic

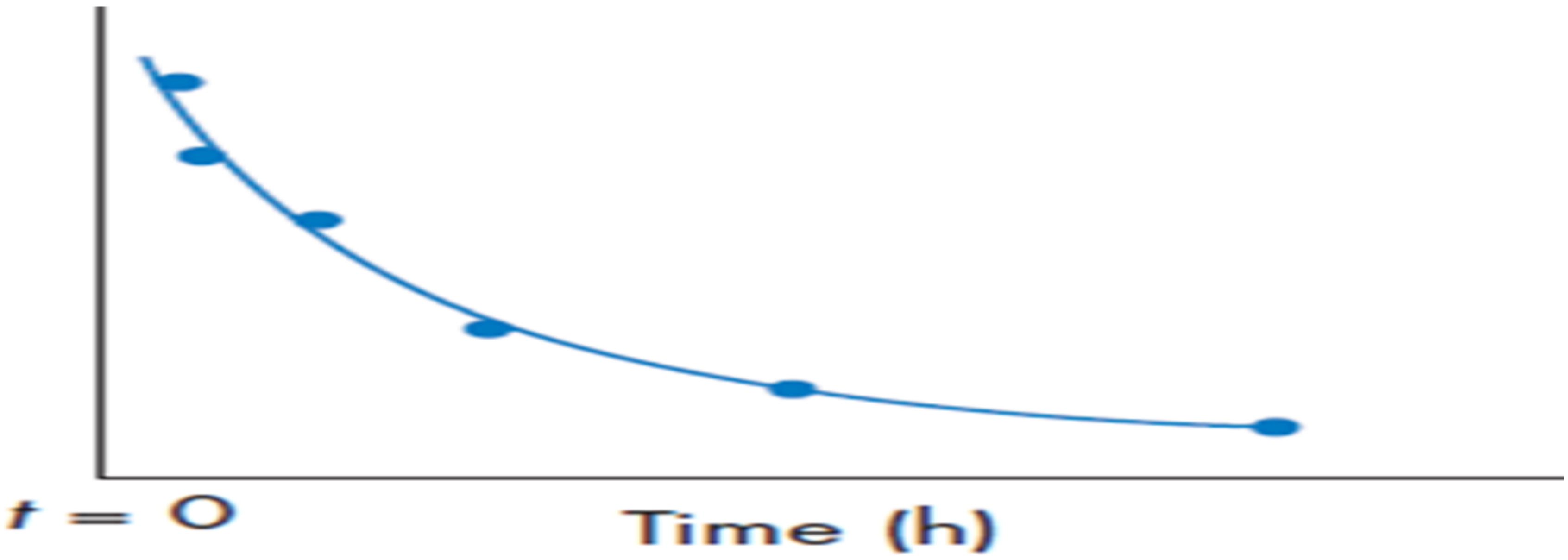


*لأنه بتناقص كنسبة وليس كمية ثابتة طلع
هيك الشكل

banana shape or curve shape

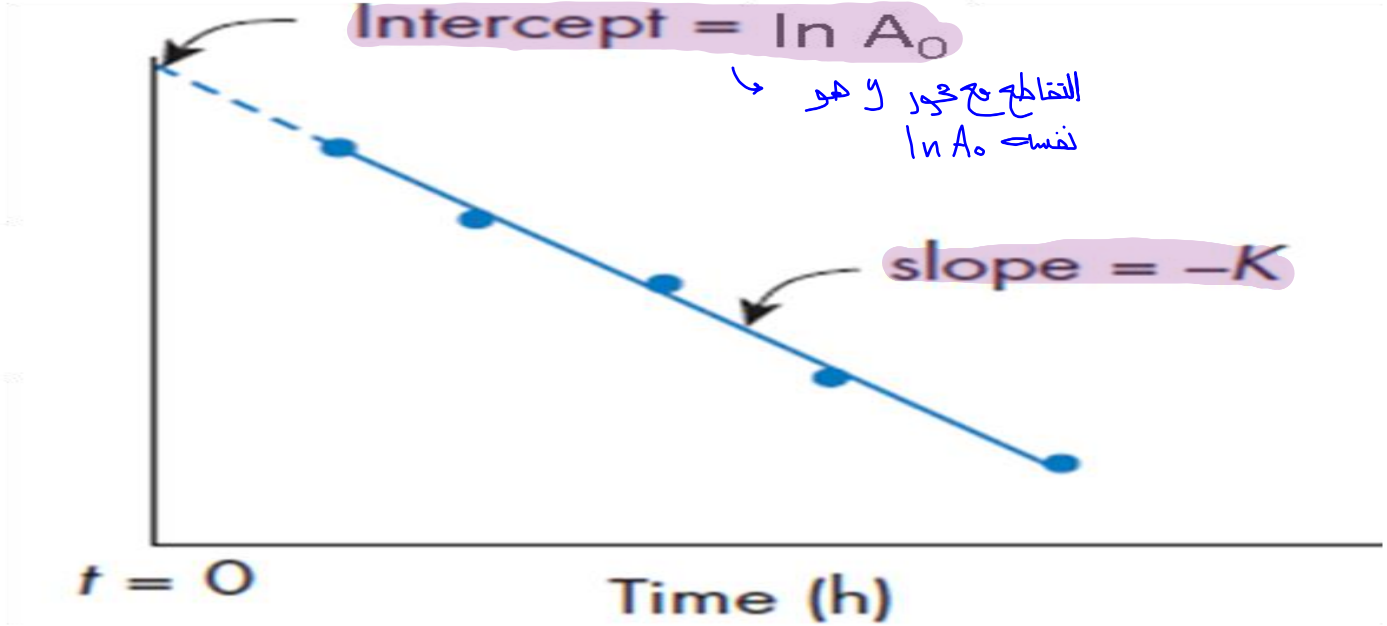
Rectangular coordinate graph

$$A = A_0 * e^{(-kt)}$$



Semilog coordinate graph

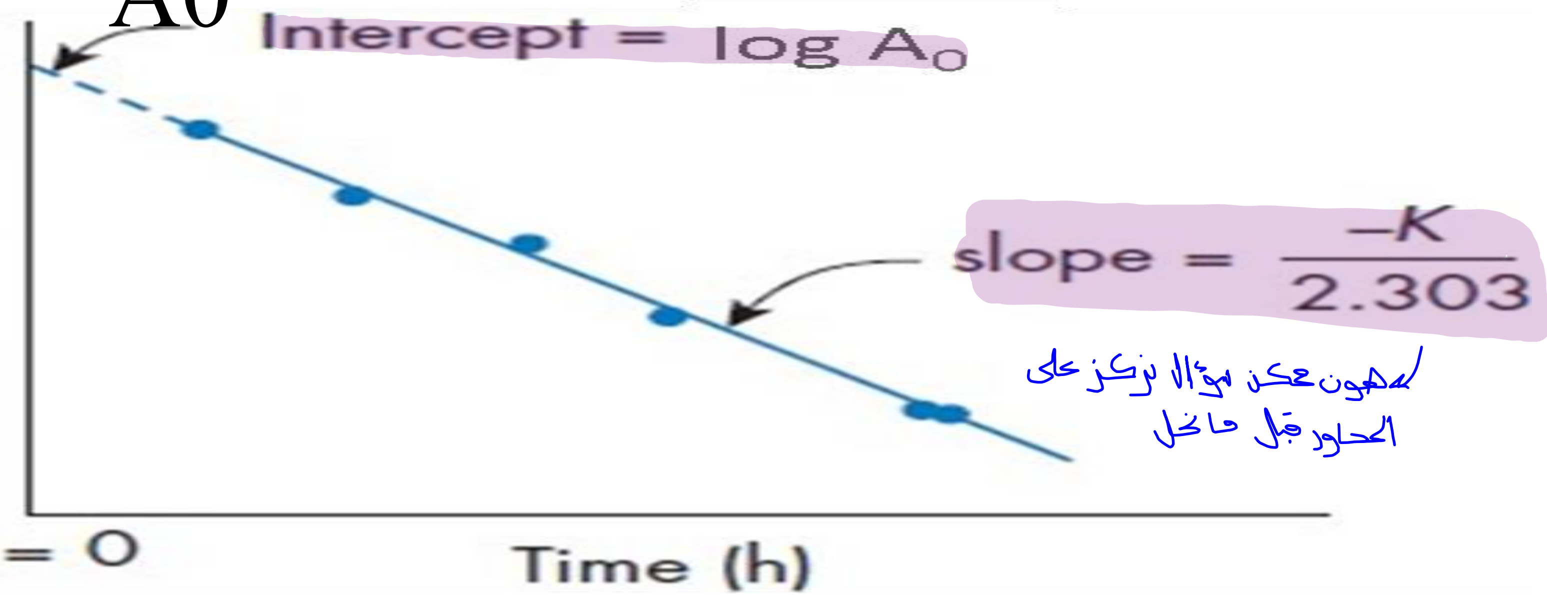
$$\ln A = - k * t + \ln A_0$$



Semilog coordinate graph

$\log A = -(k*t/2.303) + \log A0$

log A



لهون عكس سؤال نركز على
المحاور قبل ما نحل

cont

concentration=amount (A)

$$dC/dt = - k*C \qquad C = C_0 * e^{(-kt)}$$

$$\ln C = - k*t + \ln C0$$

$$\log C = - (k*t/2.303) + \log C0$$

- **C, k, C0:**

cont

- The period of time required for the amount (A) or concentration (C) of a drug to decrease by one-half.

لـ تعريف عن النصف

$$Ln A = -Kt + Ln A^0$$

$$Ln 0.5A_0 = -Kt + Ln A^0$$

$$Ln 0.5 + Ln A^0 - Ln A^0 = -Kt \Rightarrow -0.693 = -Kt \Rightarrow t = \frac{-0.693}{-K} = 0.693/K$$

- First-order half-life:

t half constant because of elimination rate constant is constant

$$t\ ½ = 0.693/\ k$$

ثابت ثابت

- $t_{1/2}$ is a constant. No matter what the initial A or C

- **The time required for the amount to decrease by one-half is CONSTANT**

compre between zero order and first order:
elimination rate constant is constant always in two order
elimination rate is constant in zero order while first order is not constant because of depend on amount
t half in first order is constant while in zero order is not constant

BEHIND EVERY SUCCESSFUL PERSON, THERE'S A LOT OF UNSUCCESSFUL YEARS

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THANK YOU
ANY QUESTIONS?