تفريغ كاينتك

محاضرة: lec 5

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لجان الدُّفعات

Soul Academy

PK parameters cases and examples

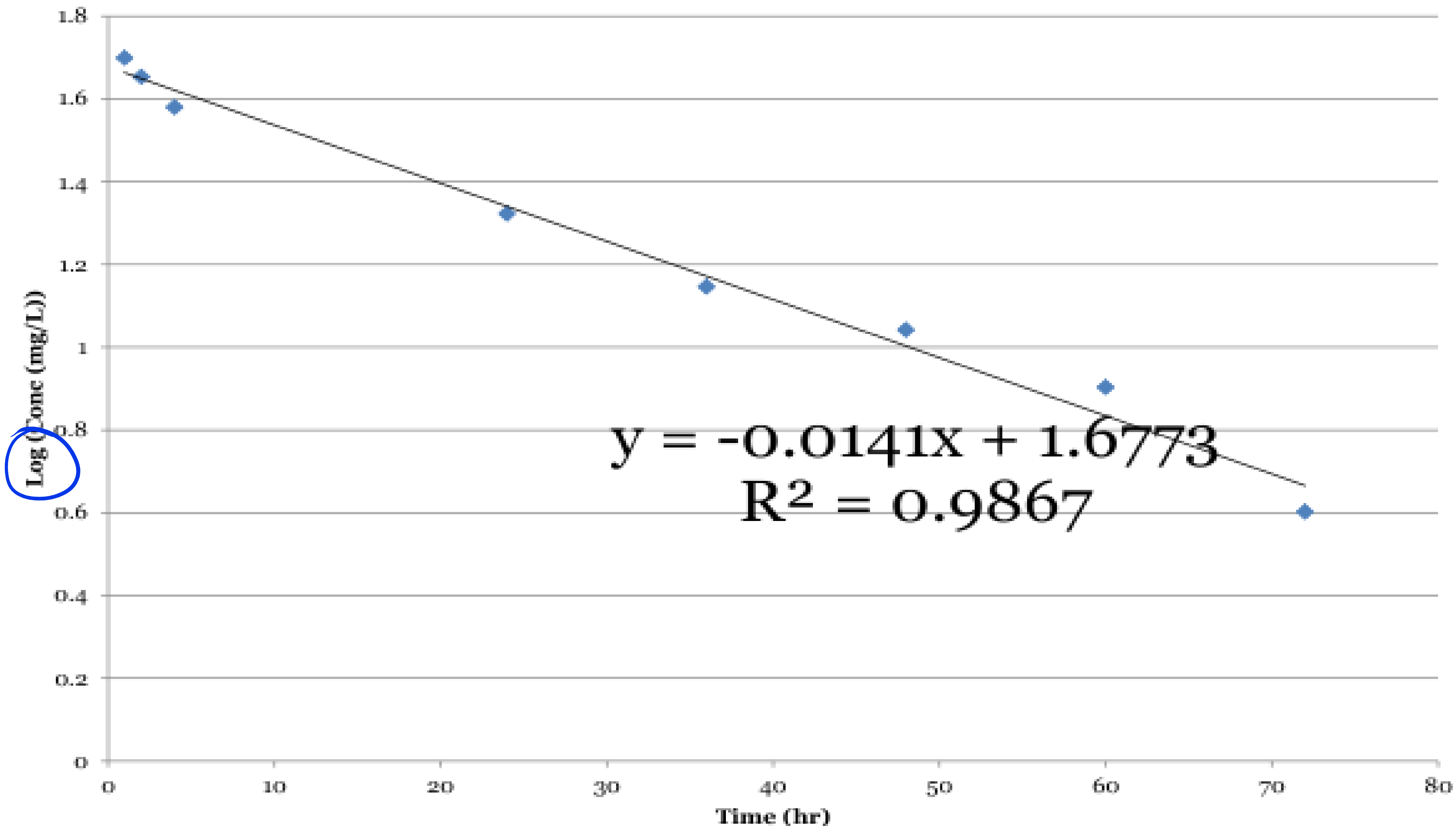
PK theory lec. 5

Example 1

- Ceftazidime is a third generation cephalosporin which is administered parenterally. In this study, eight patients with chronic renal failure were each given A_0 **1 g** of ceftazidime intravenously. Blood samples were taken the data obtained from the study is summarized in the table next slide, calculate the following"

1. The elimination rate constant K
2. The half life $t_{1/2}$
3. Find initial concentration C_0
4. Find the volume of distribution V_d
5. Find the clearance Cl
6. Find the Area Under the Curve AUC
7. Find % AUC extra

Time (h)	Concentration (mg/L)
1	50
2	45
4	38
24	21
36	14
48	11
60	8
72	4



1.8
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
Log (Conc (mg/L))
y = -0.0141x + 1.6773
R² = 0.9867
0
10
20
30
40
50
60
70
80
Time (hr)

Example 1

-2.303

1) $K = -0.2303 * -.014 = 0.0324$

2) Half- life= $0.693/K$

➔ $.693/.0324 = 21.4h$

3) $Co = 10^{1.6773}$

➔ 47.57 mg/L → * كيف طلع معنا Co أقل عند C1 اللي هي 150 المفروض يكون >50 لو بعد 0.001 !

4) $VD = X_0/C_0$

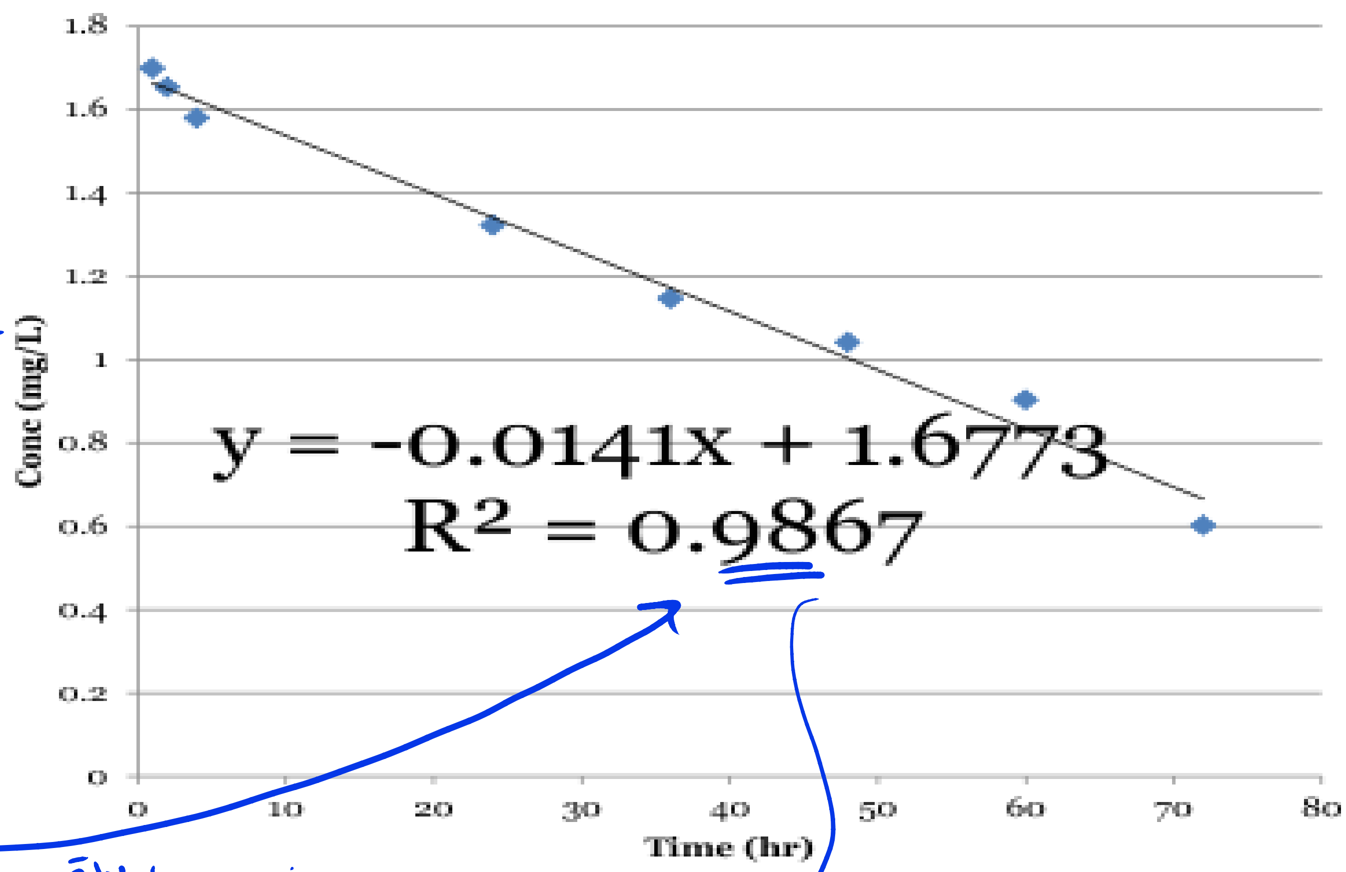
➔ $1000/47.57$ السبب هو عدم وجود curve مناسب أو غير شكل النقاط والدليل هو

➔ 21.02 L

5) $Cl = K*V = 21.02*.032$

➔ 0.67 L/h

6) See next slide



لا تساوي واحد، مما يعني إنه هاي المعادلة مش صح، ولا تنسى بالضبط ايش اللي صار.

* طب كيف أتعامل مع الموضوع؟ أزيد من العينات.
وبالتالي بقدر أرسم the best fitting line

Time (h)	Concentration (mg/L)	AUC of trapezoids
0	47.57	
1	50	48.79
2	45	47.50
4	38	83.00
24	21	590.00
36	14	210.00
48	11	150.00
60	8	114.00
72	4	72.00
	AUC last	123.5 (4/.0324)
	%AUC extra	=8.6%
	Sum	1438.74

$AUC_{last} = C_{last}/K$

Example 2

- Ten mg metoclopramide was administered intravenously to a 72 kg patient. The minimum plasma concentration required to cause significant enhancement of gastric emptying is 50 ng/mL. The following plasma concentrations were observed after analysis of the specimen.

Example 2

Time (hr)	Conc. (ng/ml)
1	90.0
2	68.0
4	40.0
6	21.5
8	12.0
10	7.0

Example 2

- Calculate the
1) half-life of the drug elimination (t½)
2) the overall elimination rate constant (K)
3) the volume (Vd) and the coefficient of distribution
4) Duration of action (td)
5) Fraction of drug eliminated at t=6 hr

remaining بدل

$\log C = 0.1243x + 2.0832$

$\log C = -\frac{K}{2.303} t + \log C_0$

① $\frac{K}{2.303} = 0.1243$ $K = 0.286\ hr^{-1}$

② $t_{1/2} = \frac{0.693}{0.286} = 2.42\ hr$

③ $Vd = \frac{A_0}{C_0}$ $\log C_0 = 2.0832$ → $C_0 = 121.12\ ng/ml$

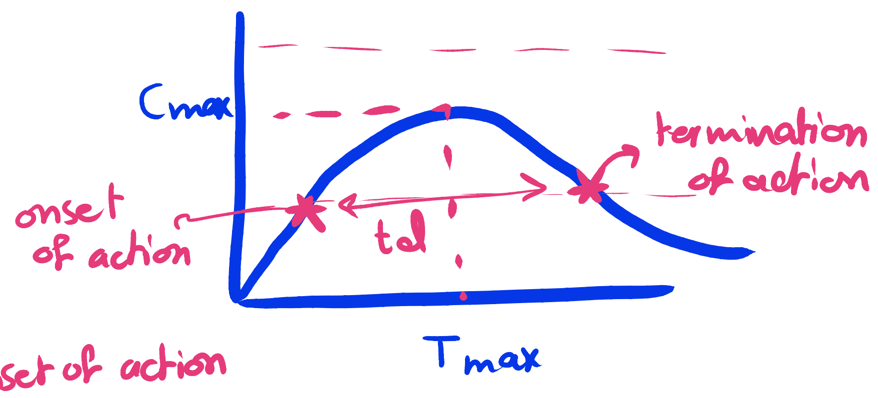
وهاد الرقم منطقي لأنه $C_1 = 90$

$= \frac{10\ mg}{121.12\ ng/ml} \times \frac{10^6\ ng}{mg} \times \frac{L}{10^3\ ml}$

$= 83\ L$

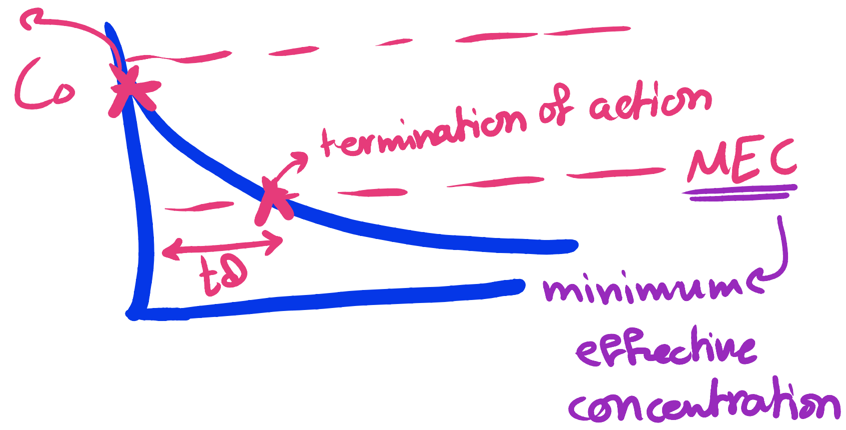
③ $Vd\ coefficient = \frac{L}{weight} = \frac{83}{72} = 1.15\ L/kg$

Oral



(IV في) onset of action

IV



td : time needed to drop from Co to termination of action

④ $t = \ln(C_0/C_*)/K$

$= \ln(121.12/50)/0.286 = 3.1\ hr$

معناها أنا بحاجة إلى 3 ساعات حتى أنزل من Co إلى termination of action

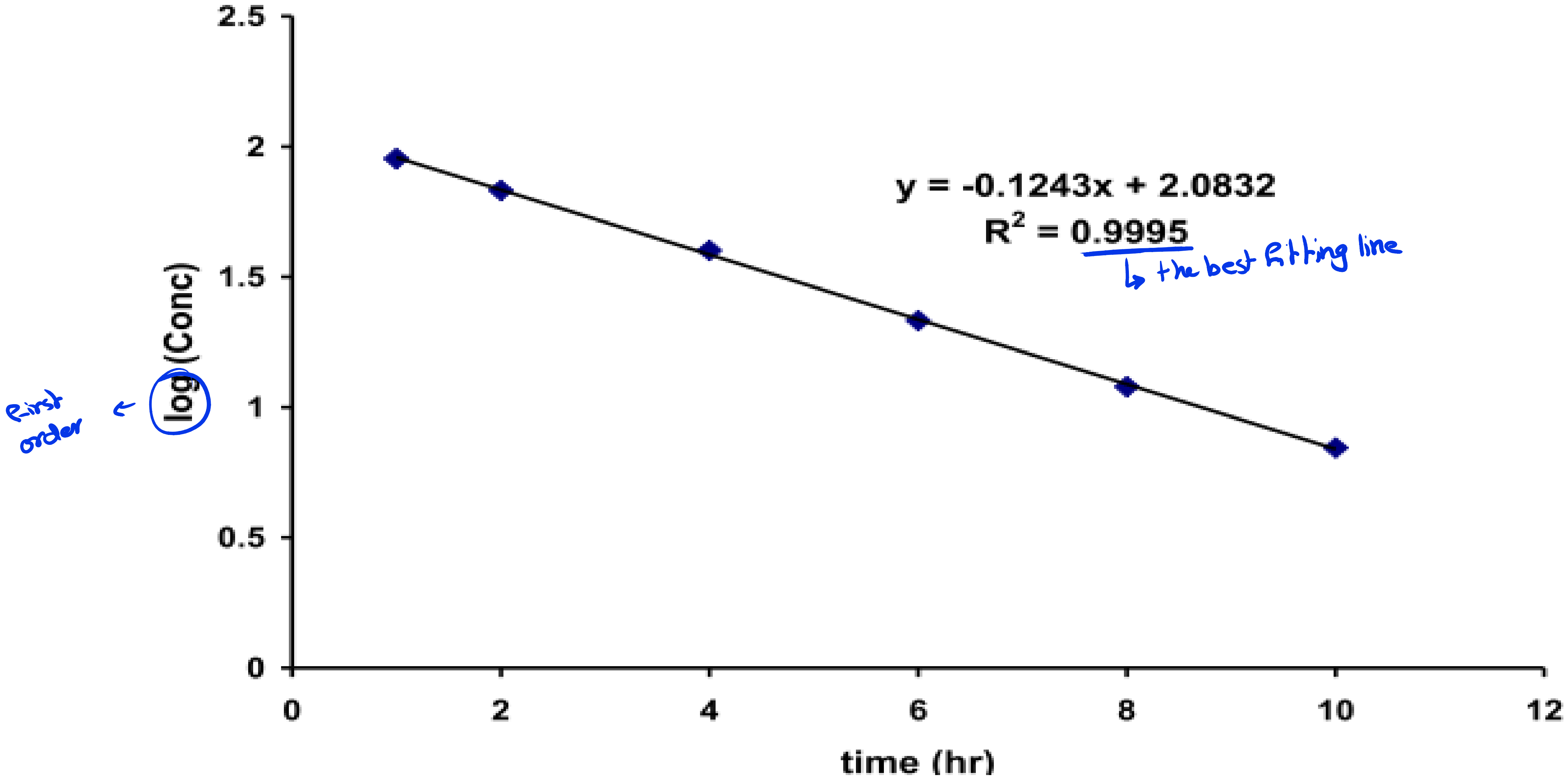
أو ما هو duration of action.

⑤ $n = t/t_{1/2} = 6/2.42 = 2.47$

$F = (0.5)^n = 0.5^{2.47} = 0.18$ remaining

eliminated = $1 - 0.18 = 0.82$

Example 2



y = -0.1243x + 2.0832
R2 = 0.9995
the best fitting line
log (Conc)
first order
time (hr)
2.5
2
1.5
1
0.5
0
0
2
4
6
8
10
12

Example 2

- The elimination rate constant can be obtained from the slope:

$$K = -\text{Slope} \cdot 2.303$$
$$= (0.1243) \cdot (2.303) = 0.286\ \text{hr}^{-1}$$

- Another way to calculate the slope is using:

$$\text{Slope} = \frac{\log(C1) - \log(C2)}{t1 - t2}$$

Example 2

- Another way to calculate the slope (if you do not have the ability to do regression) is using:

$$\text{Slope} = \frac{\log(C1) - \log(C2)}{t1 - t2}$$

  where (C1,t1) and (C2,t2) are two different conc. time points

- It is important to note that the first method for calculating the slope is more **accurate**

Example 2

- the biological half-life of the drug elimination (t½):

$$t_{0.5} = \frac{0.693}{K} = \frac{0.693}{0.286} = 2.42\,\text{hr}$$

- The volume of distribution (Vd):

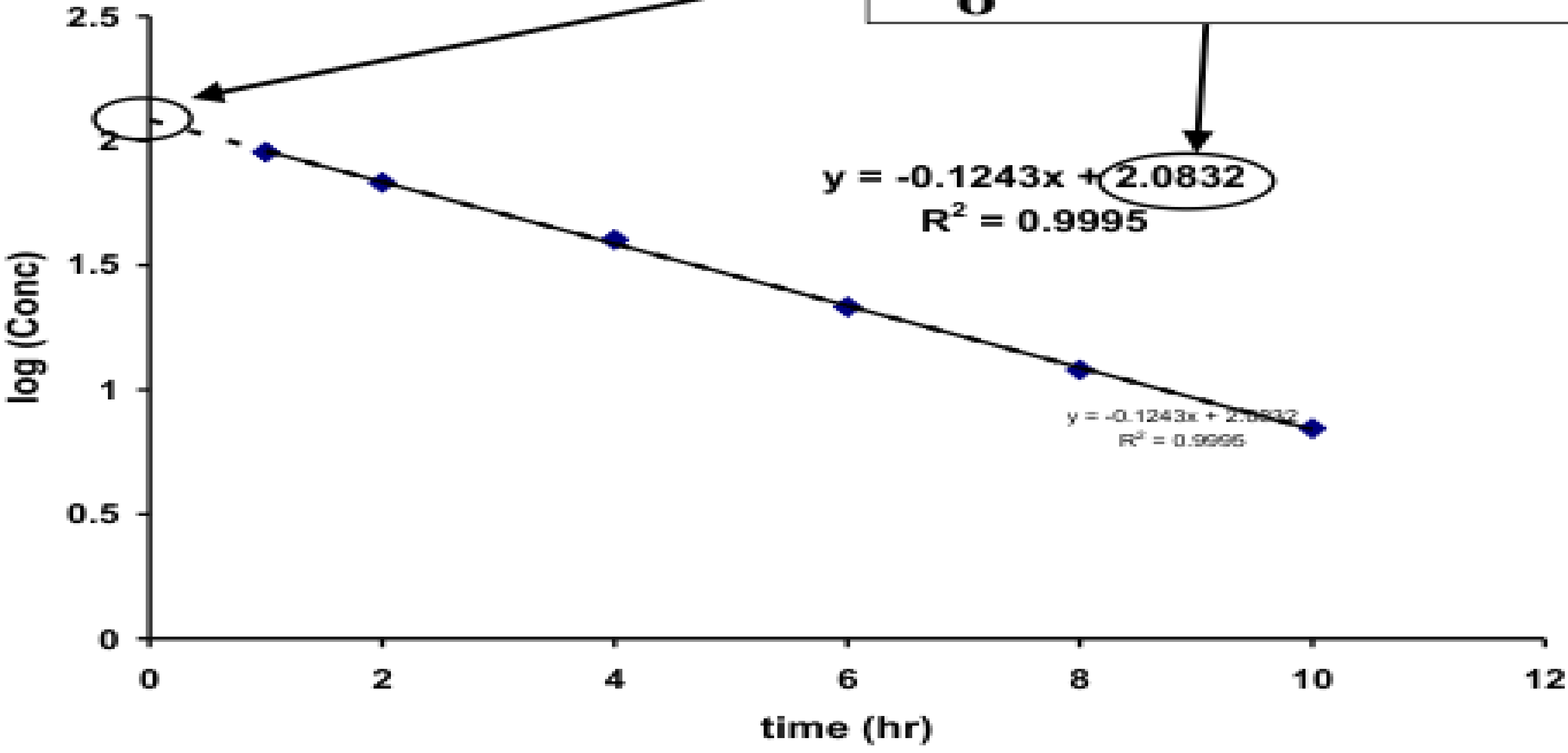
$$Vd = \frac{\text{dose}}{C_0} = \frac{10}{10^{2.0832}} = \frac{10}{121.12}$$

$$= 0.083\,\frac{\text{mg}}{\text{ng/ml}} \cdot \frac{10^6\,\text{ng}}{\text{mg}} \cdot \frac{\text{L}}{10^3\,\text{ml}} = 83\,\text{L}$$

Example 2

Intercept = log (C_o)

$C_o = 10^{intecept}$



Example 2

- the coefficient of distribution = Vd/wt
  =83 L/ 72 kg= 1.15 L/kg

- the duration of action (td). td is the time needed for the conc. To get to 50 ng/ml :

$$t = \ln\left(\frac{C_0}{C^*}\right) \Big/ K = \ln\left(\frac{121.12}{50}\right) \Big/ 0.286 = 3.1\,hr$$

Example 2

Fraction eliminated at t=6 h:

$$Fr(remaining) = (1/2)^n \implies n = 6/2.42 = 2.47$$

$$Fr = 0.18$$

$$Fe = 1 - .18 = 0.82$$

Example 3

- An adult male patient was given the first dose of an antibiotic at 6:00 AM. At 12:00 noon the plasma level of the drug was measured and reported as 5 µg/ml. The drug is known to follow the one compartment model with a half-life of 6 hours. The recommended dosage regimen of this drug is **250 mg** q.i.d. the minimum inhibitory **concentration is 3 µg/ml**. Calculate the following:
    - Apparent volume of distribution
    - Expected plasma concentration at 10 AM.
    - Duration of action of the first dose
    - Total body clearance
    - Fraction of the dose in the body 5 hours after the injection
    - Total amount in the body 5 hours after the injection
    - Cumulative amount eliminated 5 hours after the injection
    - Total amount in the body immediately after injection of a second dose at 12:00 noon
    - Duration of action of first dose only if dose administered at 6:00 AM was 500 mg.

- An adult male patient was given the first dose of an antibiotic at 6:00 AM. At 12:00 noon the plasma level of the drug was measured and reported as 5 μg/ml. The drug is known to follow the one compartment model with a half-life of 6 hours. The recommended dosage regimen of this drug is **250 mg** q.i.d. (1×4) the minimum inhibitory (→ inhibiotic كونه) **concentration is 3 μg/ml**. Calculate the following:
  - Apparent volume of distribution (→ MEC)

($t_{1/2}$ ← half-life; A_0 ← 250 mg)

t_0: 6:00 am → t_1: 12:00 pm

10 μg/ml, 6 hr; $C_1 = 5$ μg/ml

$t_{1/2} = 6$ hr; $5 \times 2 = 10$ μg/ml

① $V_d = \frac{A_0}{C_0} = \frac{250 \text{ mg}}{10 \text{ mg/ml}} = 25$ L

$\frac{10 \mu g}{1 ml} * \frac{1 mg}{10^3 \mu g} * \frac{10^3 ml}{1 L} = 10$ mg/L

② $C_{(at\ t=4)}$ (at 10 am) $= C_0 * e^{-kt}$
$= 10 * e^{-kt}$
$= 10 * e^{-0.11*4}$
$= 6.3$ μg/ml

$K = \frac{0.693}{6} = 0.116$ hr^{-1} → * مستحيل تطلع عندك K البرمز واحد (100٪) لأنه عبارة عن (percentage) - proportion -

↳ عشان الحرف ما يكي ماسق صح المريض كده بعد 4 ساعات يكون التركيز أقل من 10 وأكثر من 5 وأقرب إلى 5

③ $t_d = \ln(C_0/C_*)/K = \ln(10/3)/0.116 = 10.42$ hr

④ $Cl = K V_d = 0.116 * 25 = 2.89$ L/hr

⑤ $n = t/t_{1/2} = 5/6 = 0.83$
$F = 0.5^{0.83} = 0.56$ remaining after 5 hr

⑥ $A = A_0 * e^{-Kt}$ (after 5 hr) $= A_{t=5} = 250 * e^{-0.116*5} = 140$ μg

أو

$e^{-Kt} * A_0 = A$
$F * A_0$
F هو نسبة ما تبقى → $0.56 * 250 = 140$ μg

$F = e^{-Kt}$

⑦ $1 - 0.56 = 0.44 * 250 = 110$ μg

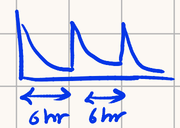
أو

$250 - 140 = 110$ μg

⑧ A at 12pm (cumulative)

A remaining 12pm + A injected 12pm
125 + 250 = 375 μg

* هاي الحالة ما انعطى المريض IV bolus انعطاه أسمي اسمها multiple dosing ورح تطلع الرسمة زي هيك



ما رح تتغير حتى لو غيرنا الـ dose لأنها خاصية ثابتة للدواء (MEC)

⑨ $t_d = \ln(C_0/C_*)/K$
$= \ln(20/3)/0.116 = 16.42$

$C_0 = \frac{A_0}{V_d} = \frac{500}{25} = 20$ mg/L

Example 3

- Apparent volume of distribution:
  C(t=6hrs)= 5 ug/ml. Since the half life is 6 hrs, C_o = 10 ug/ml.

$$V_D = \frac{X_0}{C_0} = \frac{250\,\text{mg}}{10\,\frac{\mu g}{ml} \cdot \frac{10^{-3}\,\text{mg}}{\mu g}} = 25000\,\text{ml} = 25\,\text{L}$$

- Expected plasma concentration at 10 AM

$$K = 0.693/t_{0.5} = 0.693/6 = 0.1155\ hr^{-1}$$

$$C(t=4) = C_0 \cdot e^{-K \cdot t} = 6.3\,\mu g/ml$$

Example 3

- Elimination rate constant:

$$K = 0.693/t_{0.5} = 0.693/6 = 0.116\,\text{hr}^{-1}$$

- Initial concentration:
  - The conc. at 12:00 noon (6 hrs after the first dose) is 5 μg/ml:

$$C(t=6) = C_0 \cdot e^{-k \cdot t}$$

$$\Rightarrow C_0 = \frac{C(t=6)}{e^{-k \cdot t}} = \frac{5}{e^{(-0.116)\cdot(6)}} 10\,\text{ug/ml}$$

Example 3

- Duration of action of the first dose

$$t = \ln\left(\frac{C_0}{C^*}\right) \Big/ K = \ln\left(\frac{10}{3}\right) \Big/ 0.1155 = 10.42 \text{ hr}$$

- Total body clearance

$$Cl = K \cdot V_D = 2.89 \text{ L/hr}$$

- Fraction of the dose in the body 5 hours after the injection

$$F = \left(\frac{1}{2}\right)^{\frac{5}{6}} = 0.56$$

Example 3

- Total amount in the body 5 hours after the injection = (0.56)(250 mg) = 140 mg
- Cumulative amount eliminated 5 hours after the injection = dose − amount in the body = 250 − 140 = 110 mg
- Total amount in the body immediately after injection of a second dose at 12:00 noon

Total amount = amount from the first dose + amount from the second dose = 125 + 250 = 375 mg

Example 3

- Duration of action of first dose only if dose administered at 6:00 AM was 500 mg

$$t_d = 10.42\,\text{hr} + 6\,\text{hr} = 16.42\,\text{hrs}$$

- Note that 6 hrs (one $t_{0.5}$) is needed for the amount in the body to decline from 500 mg to 250 mg

Example 4

- The therapeutic range of a drug is 20-200 mg/L. After an intravenous bolus injection of 1.0 gm followed by regression analysis of the concentration of the drug in plasma (in units of mg/L) versus time (in hours), the following linear equation was obtained

$$\log Cp = 2 - 0.1t$$

- Calculate the following
  - Duration of action
  - Total body clearance
  - Rate of elimination at 2 hours

Example 4

- From the equation:

$$\log Cp = 2 - 0.1t = \log(C_0) - slope \cdot t$$

The following were estimated:

$$C_0 = 10^2 = 100\,\mathrm{mg/L}$$

$$\mathrm{K} = -\mathrm{Slope} \cdot 2.303 = (0.1) \cdot (2.303) = 0.23\,\mathrm{hr}^{-1}$$

$$\mathrm{V_D} = \frac{\mathrm{X_0}}{\mathrm{C_0}} = \frac{1000\,\mathrm{mg}}{100\,\mathrm{mg/L}} = 10\,\mathrm{L}$$

Example 4

- Duration of action:

$$t_d = \ln\left(\frac{C_0}{C^*}\right)\Big/K = \ln\left(\frac{100}{20}\right)\Big/0.23 = 7\ \text{hr}$$

- Total body clearance= K·Vd=(0.23)(10) =2.3 L/hr
- Rate of elimination at 2 hours:
- Elimination rate = Cl*C(t=2) = 2.3*63 =145 mg/hr

$$\log(Cp(t=2)) = 2 - (0.1)(2) = 1.8$$

$$\Rightarrow Cp(t=2) = 10^{1.8} = 63\ \text{mg/L}$$