



MIRACLE Academy

حركية الدواء



لجان الرِّفْعَات

PK parameters cases and examples

PK theory lec. 5

طرحا بالسلايد الي تحت معطيتك معادلة
 $y =$

Example 1

- Ceftazidime is a third generation cephalosporin which is administered parenterally. In this study, eight patients with chronic renal failure were each given **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
7. Find $\% AUC$ extra

ورقة القوانين

$$\log C_p = \log C_0 - \frac{kt}{2.303}$$

$$C = \frac{D}{Vd} e^{-kt}$$

$$C_p = C_p^0 * e^{-kt}$$

$$V_d = \frac{\text{Dose}}{C_p^0 - C_p^0}$$

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

$$V_D = \frac{D_0}{k[AUC]_0}$$

$$\text{area} = \frac{C_2 + C_1}{2} \cdot (t_2 - t_1)$$

$$K = -\text{Slope} \cdot 2.303$$

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

$$F = \left(\frac{1}{2}\right)^n$$

$$CL = \frac{\text{Rate of elimination}}{C \text{ in plasma}}$$

$$CL = kV_D$$

$$Cl = \frac{\text{dose}}{AUC}$$

$$t = \frac{\ln\left(\frac{C_0}{C^*}\right)}{K}$$

$$F = \frac{AUC_{\text{extravascular}} \times \text{Dose}_{\text{intravenous}}}{AUC_{\text{intravenous}} \times \text{Dose}_{\text{extravascular}}}$$

$$\frac{X_u^\infty}{X_0} = \frac{Ku}{K} = fe$$

$$X_u^\infty = \frac{KuX_0}{K}$$

$$\frac{X_u^\infty}{X_0} = \frac{Ku}{K} = fe$$

$$LD = Vd \cdot C_{ss}$$

$$C^* = \frac{k_0}{k \cdot Vd} (1 - e^{-kt})$$

$$\log C = \log \frac{k_0}{V_D * k} (1 - e^{-kt}) - \frac{kt}{2.303}$$

$$\log(Xu^\infty - Xu) = \log Xu^\infty - \frac{kt}{2.303}$$

$$\log \frac{\Delta Xu}{\Delta t} = \log KuX_0 - \frac{kt}{2.303}$$

$$\frac{dX}{dt} = k_0 - kX$$

$$C = \frac{k_0}{V_D * k} (1 - e^{-kt})$$

$$C_{ss} = \frac{k_0}{V_D * k}$$

$$C_{ss} = \frac{k_0}{Cl}$$

$$k_0 = X_{ss} * k$$

$$F_{ss} = 1 - \left(\frac{1}{2}\right)^{t_{1/2}}$$

$$F_{ss} = 1 - e^{-kt}$$

اولك بحط المعطيات
 بعدت بروج
 على ورقة القوانين

* [AUC] كلم جافزان معا
 ماتنصاها
 [AUC] است
 فانتج

③ من اعاد الـ +

من فتحة الـ

\log
3

$$\text{intercept} = C_0$$

لكن هنا \log

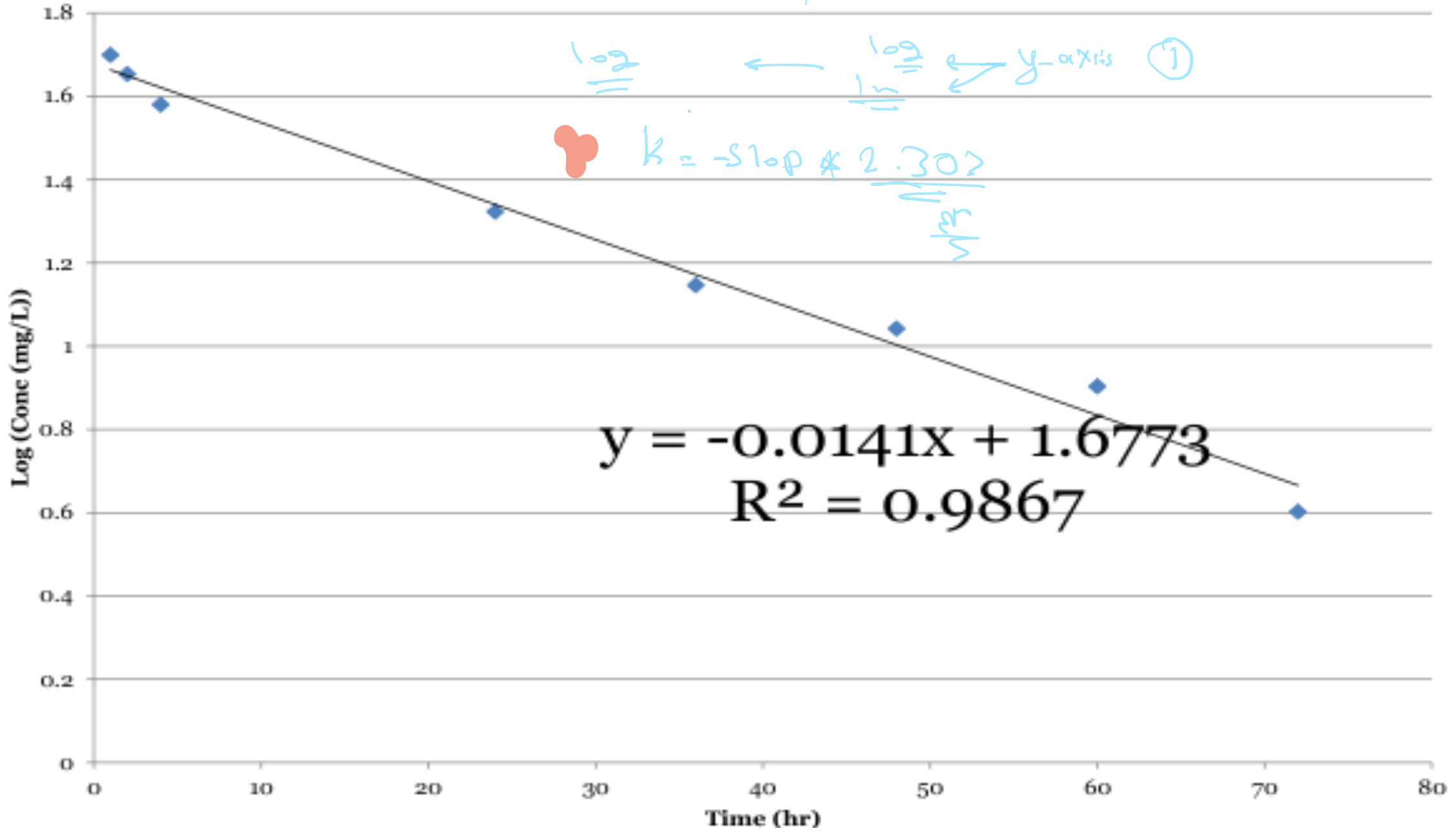
$$\log C_0 = 1.6773$$

$$\log C_0 = 1.6773$$
$$10 = 10$$

$$C_0 = 10^{1.6773}$$

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

* اولاً لما تصف الرسم البياني انصبه انه عندك



$$y = -0.0141x + 1.6773$$
$$R^2 = 0.9867$$

$k = -\text{slope} * 2.302$

Example 1

1) $K = -0.2303 \cdot -0.014 = 0.0324$

2) Half-life = $0.693/K$

→ $0.693/0.0324 = 21.4\text{h}$

3) $C_0 = 10^{1.6773}$

→ 47.57 mg/L

4) $VD = X_0/C_0$

→ $1000/47.57$

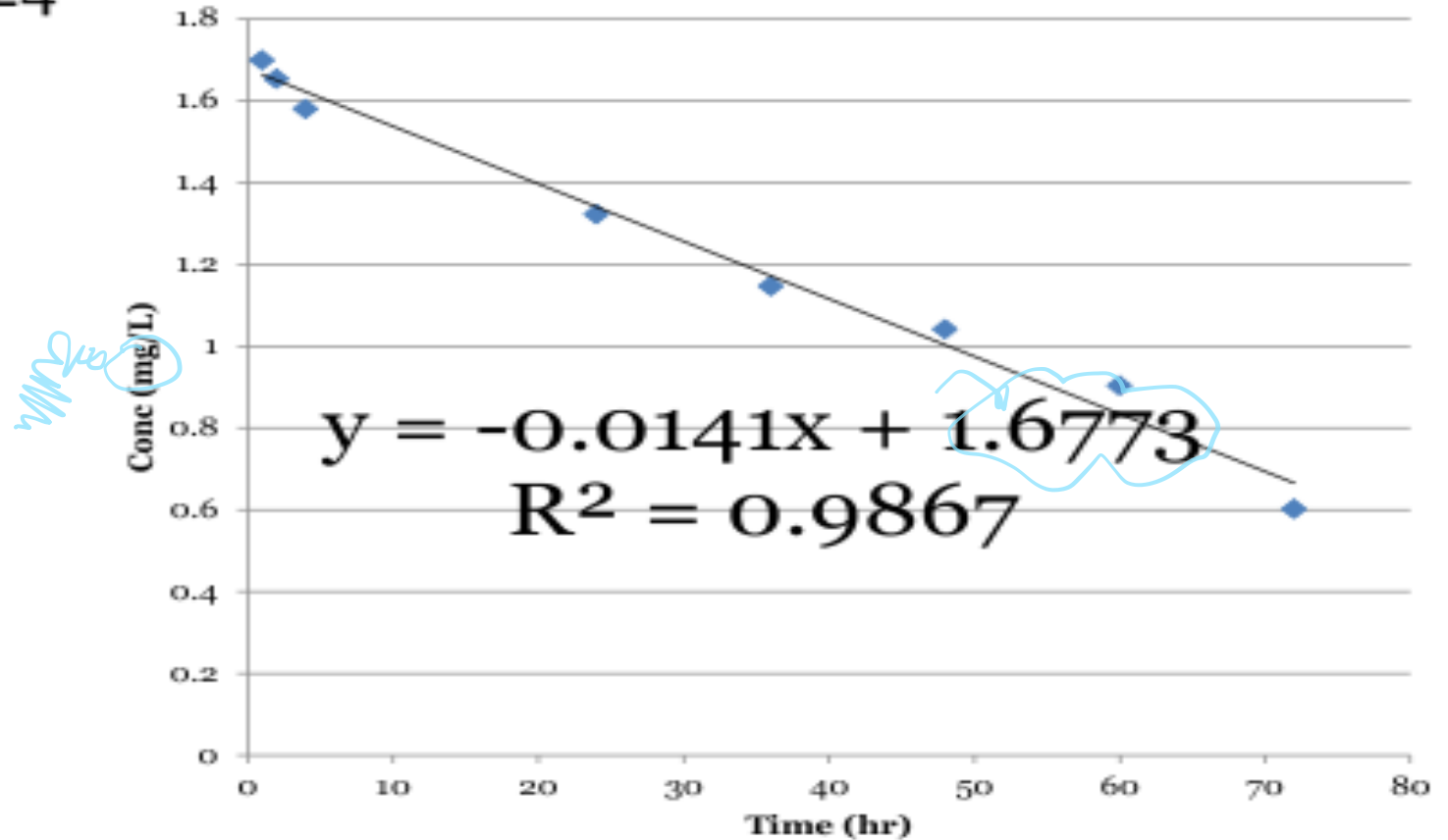
→ 21.02 L

5) $Cl = K \cdot V = 21.02 \cdot 0.032$

→ 0.67 L/h

6) See next slide


$C_0 = \text{intercept}$



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
	$C_{last(4)}$	AUC last 123.5 (4/.0324)
	k	%AUC extra = 8.6%
	$\frac{[AUC]_{last}}{[AUC]_{total}} * 100\%$	Sum 1438.74

Example 2

$$* \underline{10^3} * \underline{10^6}$$

-  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

طایعاتی در دست بیان

- Calculate the
 - 1) half-life of the drug elimination ($t^{1/2}$)
 - 2) the overall elimination rate constant (K)
 - 3) the volume (V_d) and the coefficient of distribution
 - 4) Duration of action (t_d)
 - 5) Fraction of drug eliminated at $t=6$ hr

$L/B_0 \rightarrow 72$

طایعات مرتبه و استخوان

جزء 5

! C_0 هنا ؟

&

من عين بعينها هو
(لحاجه)

$\log C_0 = \text{intercept}$

تصديق
حاصل
بتحطها

المستوفى $\log C_0 = 2.0832$

CURVE

2.0832

$C_0 = 10$

كيف نكملت \log هنا طريق

$\log 10 = 1$
الاساس

$$\log C_p = \log C_0 - \frac{k}{2.303} t$$

$$\log C_p = \log C_0 - \frac{Kt}{2.303}$$

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

$$C_p = C_p^0 * e^{-kt}$$

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

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

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

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

$$\text{area} = \frac{C_2 + C_1}{2} \cdot (t_2 - t_1)$$

$$\text{area} = \frac{C_2 + C_1}{2} \cdot (t_2 - t_1)$$

$$K = -\text{Slope} \cdot 2.303$$

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

$$F = \left(\frac{1}{2}\right)^n$$

$$F = \left(\frac{1}{2}\right)^n$$

CL = Rate of elimination
C in plasma

$$Cl = kV_D$$

$$Cl = \frac{\text{dose}}{AUC} \cdot t$$

$$Cl = \frac{\text{dose}}{AUC}$$

$$t = \frac{\ln\left(\frac{C_0}{C^*}\right)}{K}$$

$$F = \frac{AUC_{\text{extravascular}}}{AUC_{\text{intravenous}}} \times \frac{\text{Dose}_{\text{intravenous}}}{\text{Dose}_{\text{extravascular}}}$$

$$\frac{X_u^\infty}{X_0} = \frac{Ku}{K} = fe$$

$$\frac{X_u^\infty}{X_0} = \frac{Ku}{K} = fe$$

$$X_u^\infty = \frac{KuX_0}{K}$$

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$$LD = Vd \cdot C_{ss}$$

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$$C^* = \frac{k_0}{k \cdot Vd} (1 - e^{-kt})$$

$$\log C = \log \frac{k_0}{V_D * k} (1 - e^{-kt}) - \frac{kt}{2.303}$$

$$\log(Xu^\infty - Xu)$$

$$\log(Xu^\infty - Xu) = \log Xu^\infty - \frac{Kt}{2.303}$$

$$\log \frac{\Delta Xu}{\Delta t} = \log KuX_0 - \frac{Kt}{2.303}$$

$$\frac{dX}{dt} = k_0 - kX$$

$$\frac{dX}{dt} = k_0 - kX$$

$$C = \frac{k_0}{V_D * k} (1 - e^{-kt})$$

$$C_{ss} = \frac{k_0}{V_D * k}$$

$$C_{ss} = \frac{k_0}{Cl}$$

$$C_{ss} = \frac{k_0}{Cl}$$

$$k_0 = X_{ss} * K$$

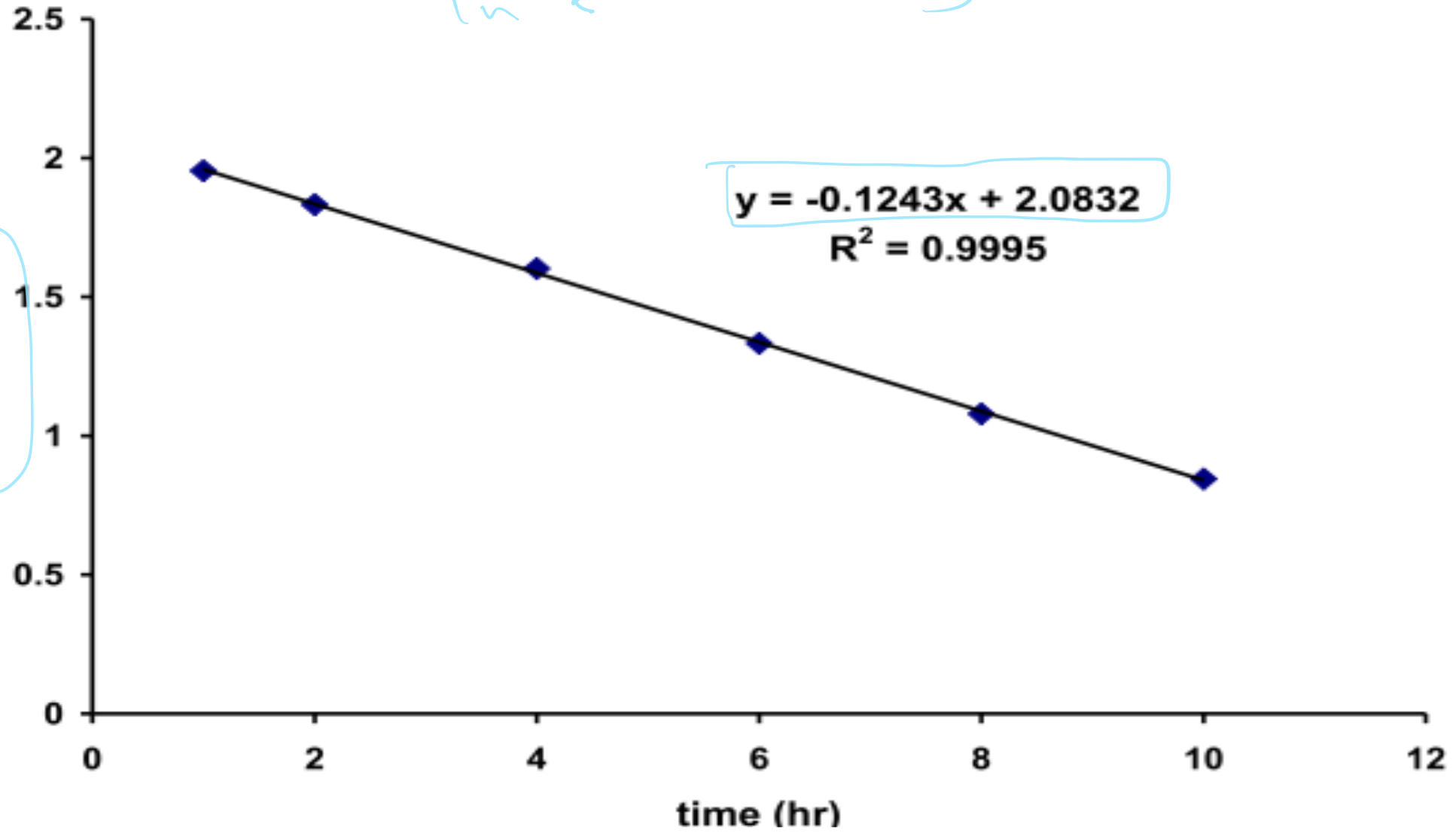
$$F_{ss} = 1 - \left(\frac{1}{2}\right)^{t/0.5}$$

$$F_{ss} = 1 - e^{-Kt}$$

Example 2

Handwritten notes in blue ink: \log (circled), \ln (with arrow pointing to the curve), and "Curve" (with arrow pointing to the curve).

Handwritten note in blue ink: $\log(\text{Conc})$ (circled).



$y = -0.1243x + 2.0832$
 $R^2 = 0.9995$

Example 2

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

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

- 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 ($t^{1/2}$):

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

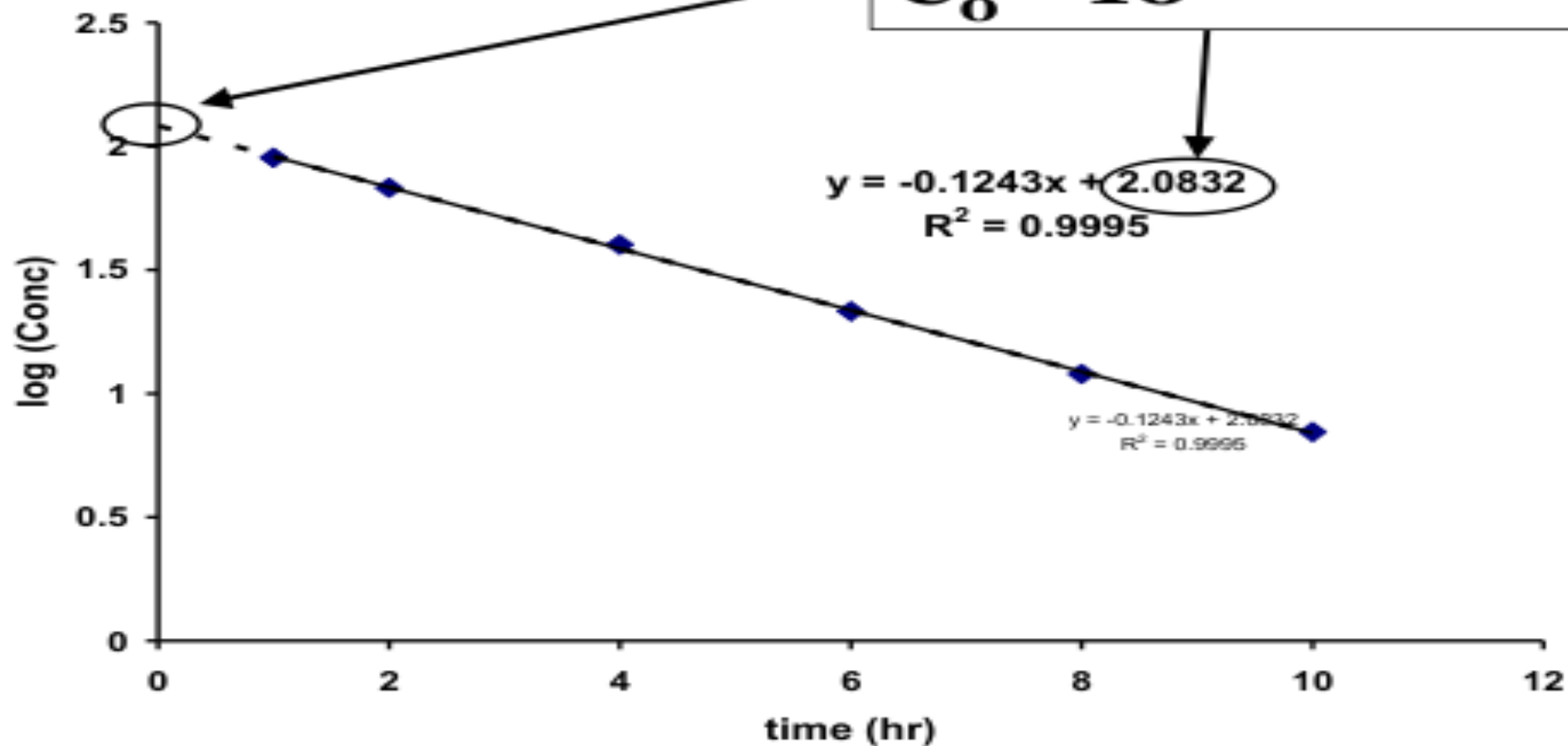
- The volume of distribution (Vd):

$$\begin{aligned} V_d &= \frac{\text{dose}}{C_0} = \frac{10}{10^{2.0832}} = \frac{10}{121.12} \\ &= 0.083 \frac{\text{mg}}{\text{ng/ml}} \cdot \frac{10^6 \text{ ng}}{\text{mg}} \cdot \frac{\text{L}}{10^3 \text{ ml}} = 83 \text{ L} \end{aligned}$$

Example 2

Intercept = $\log(C_0)$

$C_0 = 10^{\text{intercept}}$



Example 2

- the coefficient of distribution = Vd/wt
 $= 83 \text{ L} / 72 \text{ kg} = 1.15 \text{ L/kg}$

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

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

Example 2

Fraction eliminated at $t=6$ h:

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

$$Fr = 0.18$$

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

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**.

بعد 6 ساعات

Handwritten mathematical formulas for pharmacokinetics:

- $\log C_p = \log C_0 - \frac{kt}{2.303}$
- $C = \frac{D}{Vd} e^{-kt}$
- $C_p = C_p^0 * e^{-kt}$
- $V_0 = \frac{Dose}{C_p^0}$
- $\frac{dD_p}{dt} = -kD_p$
- $V_0 = \frac{D_0}{k[AUC]_0}$
- $area = \frac{C_1 + C_2}{2} (t_2 - t_1)$
- $K = -Slope \cdot 2.303$
- $t_{1/2} = \frac{0.693}{K}$
- $F = \left(\frac{1}{2}\right)^n$
- CL = Rate of elimination
- $CL = k V_d$
- $Cl = \frac{dose}{AUC}$
- $r = \frac{\ln \left(\frac{C_1}{C_2}\right)}{K}$
- $F = \frac{AUC_{intravenous} \times Dose_{extravenous}}{AUC_{extravenous} \times Dose_{intravenous}}$
- $\frac{X_u^\infty}{X_0} = \frac{Ku}{K} = fe$
- $\frac{X_u^\infty}{X_0} = \frac{KuX_0}{K}$
- $\frac{X_u^\infty}{X_0} = \frac{Ku}{K} = fe$
- $LD = Vd \cdot C_{50}$
- $C^* = \frac{k_0}{k \cdot Vd} (1 - e^{-kt})$
- $\log C = \log \frac{k_0}{Vd \cdot k} (1 - e^{-kt}) - \frac{kt}{2.303}$
- $\log(X_u^\infty - X_u) = \log X_u^\infty - \frac{kt}{2.303}$
- $\log \frac{\Delta X_u}{\Delta t} = \log KuX_0 - \frac{kt}{2.303}$
- $\frac{dX}{dt} = k_0 - kX$
- $C = \frac{k_0}{Vd \cdot k} (1 - e^{-kt})$
- $C_{ss} = \frac{k_0}{Vd \cdot k}$
- $C_{ss} = \frac{k_0}{Cl}$
- $k_0 = X_{ss} * k$
- $F_{ss} = 1 - \left(\frac{1}{2}\right)^n$
- $F_{ss} = 1 - e^{-kt}$

unclemonstrated

500 → 250

ال

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 $5 \mu\text{g/ml}$:

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

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

Example 3

- Apparent volume of distribution:
 $C(t=6\text{hrs}) = 5 \text{ ug/ml}$. Since the half life is 6 hrs,
 $C_0 = 10 \text{ ug/ml}$.

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

- Expected plasma concentration at 10 AM

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

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

Example 3

- Duration of action of the first dose

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

من الـ 10
من الـ 3
معتاد السؤال

- 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

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

Remain

Example 3

$$F * A_5$$

بقدره كمن لعل

- Total amount in the body 5 hours after the injection = $(0.56)(250 \text{ mg}) = 140 \text{ mg}$
- Cumulative amount eliminated 5 hours after the injection = dose - amount in the body = $250 - 140 = 110 \text{ mg}$
- 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 = $125 + 250 = 375 \text{ mg}$

* Total amount

half-time

First dose

250 mg at time zero

at $t_{1/2}$ = جرعة الثانية = و بعد ساعت اعطيت جرعة

فارج تكون نصف جرعة الاولى

و (total)

$$\frac{250}{2} = 125 \rightarrow$$

$$250 + 125$$

First dose

second dose ↓

time zero

time after 6

ترك سؤال بالفرع Fraction in b=2y5h والفرع اي بعده ...

انا لا اطلب Fraction غير ط (طلب) عند Amount remaining غير

يوم اطلب منك Amount eliminated

$$F = \left(\frac{1}{2}\right)^n$$

Amount remaining F_r * Amount initial (A_0)

$$A_{\text{eliminated}} = A_0 - A_{\text{r remaining}}$$

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

طای
من الفریق
3

نصفها
250
action إذا $\frac{6}{10.9246} = t_{1/2}$

جا

طريقة اخرى
لحساب ملي ماخو
 $t = \ln\left(\frac{C_0}{C_t}\right)$
من السؤال
500

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

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

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

Example 4

- From the equation:

$$\log C_p = 2 - 0.1t = \log(C_0) - \text{slope} \cdot t$$

The following were estimated:

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

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

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

Example 4

- Duration of action:

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

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

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

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