

Example 3 ما يعرف Conc. كالمادة

→ ك العلاج

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 دواء
- Expected plasma concentration at 10 AM. يوجد ساعة واحدة بعد الجرعة
- 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.

Example 3

من 6am → 12noon T half
 5 = Conc. و
 10 = 5 + 5 = C₀ = بعضها الوقت

• Elimination rate constant:

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

• Initial concentration:

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

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

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

$$K = \frac{0.963}{6} = 0.1605$$

+ half

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

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

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

Handwritten work for the concentration calculation:

$$e^{-0.462} = 10 * e^{-0.1155 * 4}$$

$$\ln = \ln(10 * e^{-0.462})$$

$$\ln = -0.462 = 6.3$$

Arabic note: صفة الفرع ابى قبله

Example 3

- Duration of action of the first dose

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

- Total body clearance

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

$$K = \frac{0.693}{6}$$

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

$$n = \frac{t}{t_{1/2}}$$

$$= \frac{5}{6}$$

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

$$F = e^{-Kt} = e^{-\frac{0.693}{6} * 5} = 0.56$$

Example 3

remain
 • Total amount in the body 5 hours after the injection = $(0.56)(250 \text{ mg}) = 140 \text{ mg}$

الكمية التي طلعت
 • 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 = $125 + 250 = 375 \text{ mg}$

$F = \left[\frac{1}{2}\right]^{\frac{6}{6}} = \frac{1}{2} \times 250 = 125$

$C_0 = \frac{C_0}{C}$

$F_{eliminated} = 1 - F_{remaining}$

$1 - 0.2$

parameters لا يتغير
 AUC
 $T_{1/2}$
 K
 Vd
 CL

Example 3

MIC السؤال هو C^* ثابتة
 • Duration of action of first dose only if dose administered at 6:00 AM was 500 mg

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

$C_0 = \frac{D_0}{V_d} = \frac{500}{25} = 20 \text{ mg/L}$

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

$T = \frac{-\ln C_0/C^*}{K}$

$= \frac{-\ln 20/3}{0.693/6}$

كل $T_{1/2}$ يتطلع نصف الكمية
 500mg لحد ما نزلت لـ 3mg
 250 ← 500
 Second dose
 6 hours ← من السؤال
 Duration of action of first dose
 3mg ← 250
 10.42 + 6 =
 16.42 =

Example 4

IV أقل ما MTC ف C₀ لا يزيد عن 20 وأقل من 20
 MTC و MEC
 إذا لا حتى خطأ

MEC MTC

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

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

$$\frac{k}{2.303}$$

المعادلة مباشرة الحل

• Calculate the following

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

إذا كانت k

$$0.1 = k$$

علاقتها

$$0.1 = \frac{k}{2.303}$$

$$k = 0.1 \times 2.303$$

$$k = 0.2303$$

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

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

ربط المعادلة الأصلية

Example 4

• From the equation:

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

The following were estimated:

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

$$\log C_p = 2$$

$$C_p = 10^2 = 100$$

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

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

Example 4

• Duration of action:

$$\frac{2.303}{0.1} = 0.23$$

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

بجانب الكمية
التي تزود

• Total body clearance = $K \cdot V_d = (0.23)(10) = 2.3$ L/hr

ما دخل K

Amount
time

or

Concentration
time

• Rate of elimination at 2 hours:
Elimination rate = $Cl \cdot C(t=2) = 2.3 \cdot 63 = 145$ mg/hr

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

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

• $Cl = \frac{\text{rate of elimination}}{\text{Concentration at specific time (2 hour)}}$

$$2.303 = \frac{X(2)}{C(2)}$$

$$\rightarrow \text{في وقت} \rightarrow C_0 \cdot e^{-kt} = 100 \cdot e^{-0.2303 \cdot 2} = 63.13$$

$$2.303 = \frac{X(2)}{63.13}$$

$$= 145$$

Slide 1

* pharmacokinetic parameters في الدم

Volume of distribution, elimination rate, clearance

* PK parameters في Urine

Urine بطريقة

$$\text{elimination rate Constant } K = K_{\text{excretion Renal}} + K_{\text{metabolism (m)}}$$

Urine في

إذا هي K و K_{renal} في معرفة K_m

* إذا هي dose, K , V_d , في معرفة K_m parameters

clearance في معرفة

إذا هي AUC في معرفة V_d إذا هي dose

* مميزات أخذ العينات في Urine Concentration في

1) non invasive

2) more convenient

Sample size in blood → 0.5-2 ml

Urine في 0.5 ml

Urine → Interval time not at specific time

الوقت في عبارة عن وقت أول العينة لحد وقت آخر عينة

مثلاً المدة بين وقت ساعة عينة و 3 ساعات عينة جديدة

في الوقت في ساعة إلى 3 ساعات إلى جمع فيهم Urine

في فيها الدواء في تتركيزه (في إلى)

blood → At specific time

* [3] Bioavailability: Amount of drug that reaches systemic circulation.

Slide 2 Bioavailability لا يتم AUC

نوعين.

ABSOLUTE

RELATIVE

* لا تقارن أديمنس route of admin مع IV

* لا تقارن 2 routs of administration

2 dosage forms لا تقارن

IV مع Oral

مثلاً suspension مع tablet

bioavailability 100% ← IV

2 oral أو 2-tablets

مباشرة الورا باله بدخل.

بني عامر generic و brand

يكون خلاها يطبقوا براءة الاختراع.

Paracy

Slide 3

* بوتوكول موحدة لأجل Urine Conc. معينه

1 لازم جزء من الورا الي به يطبع Unchanged

No metabolism.

يعني 10% من الورا يطبع Unchanged (أقل من 10%)

$$K = \frac{K_{renal}}{K_{metabolism}}$$

لو شوا كالتة K = 10% = 90% metabolites

Unchanged

لازم اقل من 10% يكون Unchanged اذا اقل فالعنه

غير كافية يعني معظم الورا صار له metabolism معظم

K هي عبارة Km

in urine

③ يكون \uparrow metabolic ما يتركز في فحوصات parent drug

④ المريض بعد النوم لازم يشرب ٣٠٠ مل ماء

fasting ← ٨ ساعات بدون ماء أو أكل

بعد أول ~~ساعة~~ ساعة لازم يفحص ال bladder كاملة

العينة بنحطها ← Blank/Control ما بي Conc. of drug

$\text{Conc. of drug} = \text{Zero}$

أنا بحسب K من IV

بعدين بقطعه دواء (IV bolus) وبعدين كل ساعة بقطعه

٣٠٠ مل لمدة ٤ ساعات. ريفل أوصد عينات.

أو اتل

⑤ لازم يرجع Urine خلال فترة $T_{1/2}$ ما بغير يتجازها

لأنه ما بقدر اخذ $T_{1/2}$ أو K .

* بخلص بتجميع عينات بعد $T_{1/2} + 7$ من الدواء.

Slide 5

$$\frac{dX}{dt} = -KX \quad \text{مغير تركيز الدواء بالدم أو بالحبيب}$$

أو بال box

$$\frac{dA}{dt} = -KA \quad \leftarrow \text{amount in blood decrease}$$

$$\frac{dB}{dt} = +KB \quad \leftarrow \text{amount in Urine increase}$$

* زيادة تركيز الدواء بال Urine هو نقصانه بالدم

Urine \downarrow k , Conc. \downarrow k طريق ~~ال~~ ~~إخراج~~ ~~ال~~ ~~دواء~~ *

① Sigma-minus method

② amount remaining to be excreted.

$$(1 - e^{-kt}) \quad (\text{كمية الدواء المتبقية - كمية الدواء التي أُخرجت})$$

X_u : amount of drug in urine at anytime.

$$X_u = \frac{k_u X_0}{k} (1 - e^{-kt}) = X_u^\infty (1 - e^{-kt})$$

$X_u^\infty = \frac{k_u X_0}{k}$

amount of drug in urine \downarrow X_u^∞ is

X_0 : total amount . at ∞ Time \leftarrow Urine

fully excreted $k_u = k$ إذا

$$\frac{k_u X_0}{k} = X_0$$

amount of drug \downarrow $X_0 = X_u^\infty$

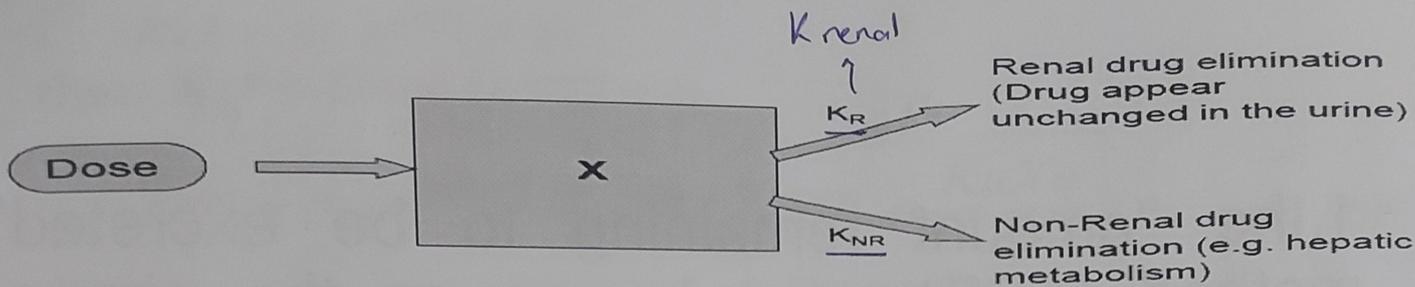
in urine , No metabolism.

$k_u \neq k$ partially metabolised.

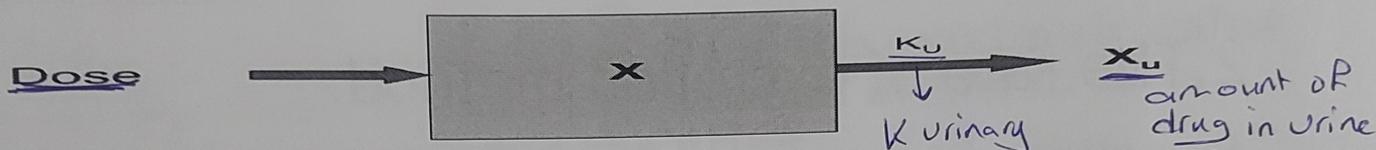
$\frac{k_u}{k}$ fraction excreted \downarrow X_u^∞ \downarrow X_0

fraction \downarrow X_u^∞ \downarrow X_0 \downarrow X_0

Renal and Non-renal elimination pathways



- A scheme of one compartment model for a drug that is eliminated exclusively by urinary excretion:



In such case the excretion rate constant (K_U) equals the elimination rate constant (K)

$K_m = 0$ K_U ~~K~~
 exclusively eliminated K_U ~~K~~
 through urine or fully eliminated through urine
 or excreted unchanged in urine.

Computing PK Parameters From Urinary Data

- It is assumed that the rate of the drug appearance in the urine (dX_u/dt) is a kinetic process occurring in a first order fashion.
- It is important to note that (dX_u/dt) **cannot** be determined experimentally for any given instant. Therefore, the average rate of urinary drug excretion, X_u/t is plotted against the average time as shown in the following slides

نرخه تركيز الدواء بال Urine هو نقصانه بالدم

تغير الدواء بالدم
بالرسم ار box

$$\frac{dX}{dt} = -KX$$

تفاضل تركيز الدواء بالدم

$$\frac{dA}{dt} = -KA$$

amount in blood
بقي

$$\frac{dB}{dt} = +KB$$

metabolite
بنت

sigma-Minus Method

• At $t = 0$; $e^{-k^*t} = 1$
 then $X_U^0 = \text{Dose} [1 - 1] = 0$

• At $t = \infty$; $e^{-k^*t} = 0 \rightarrow \boxed{X_u^\infty = \frac{K_u X_0}{K}}$

Re-arranging the above equation yields:

$$\frac{X_u^\infty}{X_0} = \frac{K_u}{K} = f_e$$

F_e is the fraction of excreted drug, the maximum value for the fractions is 1 and this is when all the drug is eliminated unchanged in the urine

Fully excreted. $\boxed{K_u = K}$ اذا

amount of drug in Urine. $\boxed{X_0 = X_u^\infty}$
 No metabolic.

$\boxed{K_u \neq K}$ Partially eliminated.
 و بعض في نسبه fraction excreted.

Cont, K_u fraction
 و جزء من K و جزء من X_0

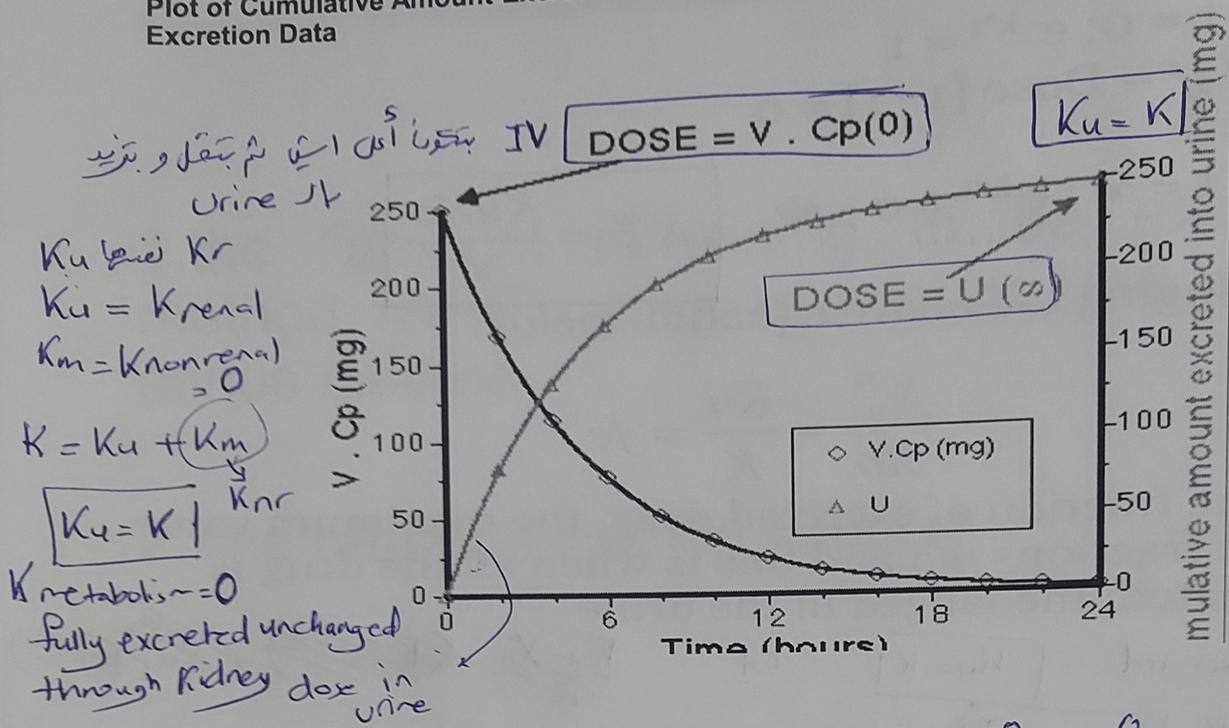
Fully excreted.

When all the drug is eliminated unchanged in the urine then $X_u^\infty = X_0$

كل amount ابي اطبقها ب
 IV bolus صارت في Urine.
 جميع Urine في $F_e = 1$ كانه في اطبقها.

$$(X_u)_t = X_0 * (1 - e^{-Kt})$$

Plot of Cumulative Amount Excreted Versus Time Comparing Plasma Data vs. Urinary Excretion Data



Amount of drug in urine at time 0 = 0

$e^\infty = 0$

At time 0
 $X_u = X_u^\infty (1 - e^{-Kt})$

Cont,

$X_u = X_u^\infty$

$K_u = \frac{K_u}{K} X_0$

Sigma-Minus Method

Fraction = $\frac{K_u}{K}$ or $\frac{X_u^\infty}{X_u}$

$\frac{K_u}{K} = 1$ هنا
 $K_u^\infty = X_0$ ههنا

$X_u = X_u^\infty (1 - e^{-Kt})$

$X_u = X_u^\infty - X_u^\infty e^{-Kt}$

$X_u^\infty - X_u = X_u^\infty e^{-Kt}$ Fraction

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

where " $X_u^\infty - X_u$ " is the amount of the drug remaining to be excreted

Remember when the drug is excreted 100% renally then $K_u = K$ and $X_u = X_0$; otherwise

هين بطرح
 $K_m = K - K_u$

$X_u^\infty = \frac{X_0 * K_u}{K}$

هه جزوه K كماله
 K_r او K_u

Intercept

Slope

example

Sigma-Minus Method (Example)

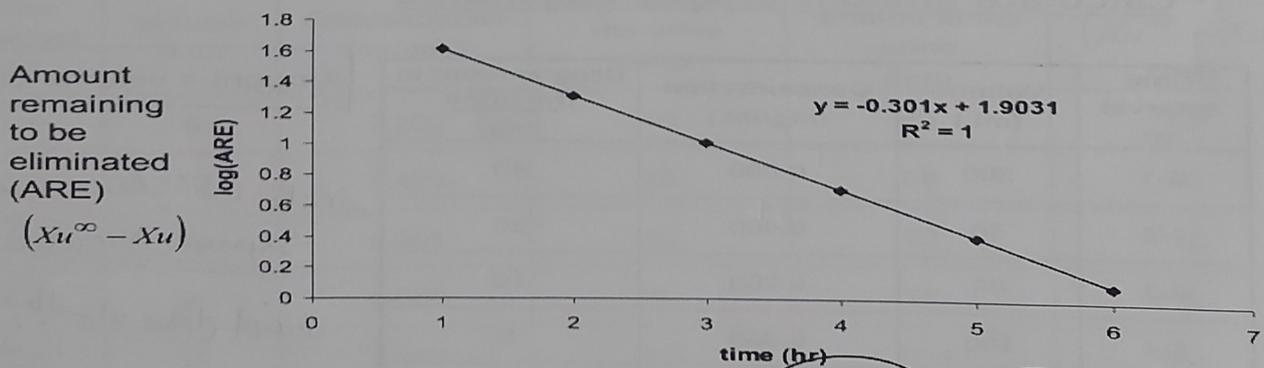
- An intravenous bolus dose of 120 mg of a drug was administered. The drug is one that is partially eliminated by urinary excretion of unchanged drug following one-compartment model distribution and first-order elimination.
- The following Table provides the urinary data in a tabulated form.

$K_u \neq K$

time interval

Cont,

Sigma-Minus Method :



Amount remaining to be eliminated (ARE)
 $(X_u^\infty - X_u)$

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

Intercept

Slope

Cont,

Sigma-Minus Method (Example)

اول اشی بوسی
 $Amount = Conc. * Volume$
 time interval

Time interval (h)	Volume (mL)	Concentration (mg/mL)
0-1	200	0.200
1-2	50	0.400
2-3	50	0.200
3-4	100	0.050
4-5	25	0.100
5-6	125	0.010
6-12	250	0.005

Cont,

$X_u^\infty \neq K$

Sigma-Minus Method :

1- Calculate amount of drug eliminated

Amount = volume * conc

Time interval (h)	Volume (mL)	Concentration (mg/mL)	Drug amount in the urine (mg)
0-1	200	0.200	40
1-2	50	0.400	20
2-3	50	0.200	10
3-4	100	0.050	5
4-5	25	0.100	2.5
5-6	125	0.010	1.25
6-12	250	0.005	1.25

هو بصدی بدو ادره
Sigma-minus Cumulative
 لا بالحوان بطرح اشدت
 بیط

partially eliminated
 completely
 $X_u^\infty \neq K$

amounts X_u^∞ ← 80

اما بدو های ادری

cont,

Sigma-Minus Method :

2- Calculate cumulative amount of drug eliminated

Time interval (h)	Volume (mL)	Concentration (mg/mL)	Drug amount in the urine (mg)	Cumulative amount in the urine (mg)
0-1	200	0.200	40	40
1-2	50	0.400	20	60
2-3	50	0.200	10	70
3-4	100	0.050	5	75
4-5	25	0.100	2.5	77.5
5-6	125	0.010	1.25	78.75
6-12	250	0.005	1.25	80

X_u^∞

درد ای بوسه کی
X axis

Cont,

Sigma-Minus Method :

3- Calculate amount remaining to excreted (ARE)

$C \cdot V$

Cumulative X_u

Time interval (h)	Volume (mL)	Concentration (mg/mL)	Drug amount in the urine (mg)	Cumulative amount in the urine (mg)	ARE ($X_u^\infty - X_u$) (mg)
0-1	200	0.200	40	40	40
1-2	50	0.400	20	60	20
2-3	50	0.200	10	70	10
3-4	100	0.050	5	75	5
4-5	25	0.100	2.5	77.5	2.5
5-6	125	0.010	1.25	78.75	1.25
6-12	250	0.005	1.25	80	0

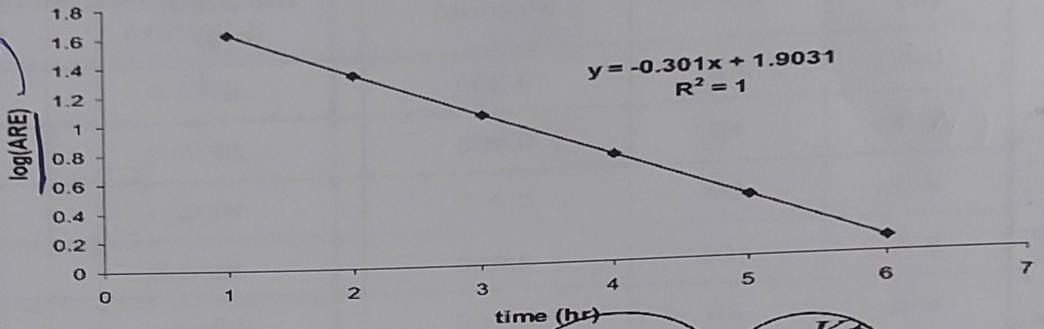
80-

Cont,

Sigma-Minus Method :

4- Plot time (end of interval) vs. log(ARE)

Time (h)	ARE ($X_u^\infty - X_u$) (mg)
1	40
2	20
3	10
4	5
5	2.5
6	1.25
12	0



$$\log(X_u^\infty - X_u) = \underbrace{\log X_u^\infty}_{\text{Intercept}} - \underbrace{\frac{Kt}{2.303}}_{\text{Slope}}$$

~~$y = -0.301x + 1.9031$~~

$$y = 1.9031 - 0.301x$$

Cont, لهذا نعلم بهاي الحاضرة نطرح K_m و K_u

Sigma-Minus Method :

5- Estimate PK parameters from the values of the slope and the intercept

$$\text{Slope} = -\frac{K}{2.303} = -0.301$$

لكننا نعلم بهاي الحاضرة نطرح K_u في المعادلة
نطلبها

$$\Rightarrow K = 0.301 * 2.303 = 0.693 \text{ hr}^{-1}$$

$$\text{Intercept} = \log X_u^\infty = \log \left(\frac{K_u}{K} \cdot X_0 \right) = 1.9031$$

$$\Rightarrow K_u = \frac{K}{X_0} \cdot 10^{\text{Intercept}} = \frac{0.693}{120} \cdot 10^{1.9031} = 0.462 \text{ hr}^{-1}$$

How about K_{nr} ?

$$K_m = K - K_{nr} = 0.231 \text{ hr}^{-1}$$

كلين K هي K_u
كلين K هي K_m

$$\frac{K_u}{K} = \frac{X_u}{X_0} = \frac{80}{120} = \frac{2}{3}$$

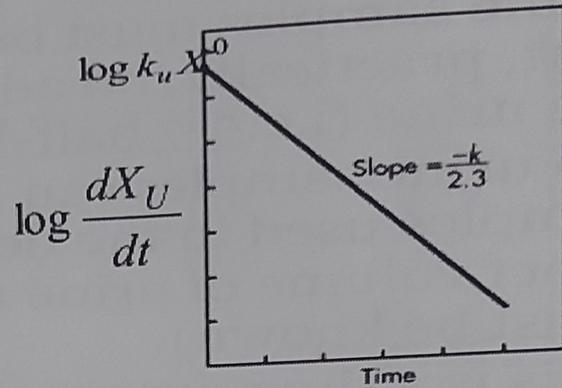
* اذا طبقت المعادلة كانت بحسب $80 = K_u^\infty$
في K_m

Cont,

The rate method

A straight line is obtained by plotting the previous equation

Therefore, if X^0 is known, the renal excretion rate constant (k_u) can be obtained



$$\log \frac{dX_U}{dt} = \frac{-kt}{2.303} + \log k_u X^0$$

example

The rate method (Example)

على نفس الجرار

- An intravenous bolus dose of 120 mg of a drug was administered. The drug is one that is partially eliminated by urinary excretion of unchanged drug following one-compartment model distribution and first-order elimination.
- The following Table provides the urinary data in a tabulated form.

cont,

The rate method (Example)

Time interval (h)	Volume (mL)	Concentration (mg/mL)
0-1	200	0.200
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2-3	50	0.200
3-4	100	0.050
4-5	25	0.100
5-6	125	0.010
6-12	250	0.005

cont,

The rate method:

1- Calculate amount of drug eliminated

Time interval (h)	Volume (mL)	Concentration (mg/mL)	Drug amount in the urine (mg)
0-1	200	0.200	40
1-2	50	0.400	20
2-3	50	0.200	10
3-4	100	0.050	5
4-5	25	0.100	2.5
5-6	125	0.010	1.25
6-12	250	0.005	1.25

Amount = volume * conc

$$\frac{\text{amount}}{\text{time}} \rightarrow \text{rate}$$
$$t_2 - t_1 \rightarrow \Delta t$$
$$\Delta x$$

Cont,

The rate method:

2- Calculate the change in time

Time interval (h)	Volume (mL)	Concentration (mg/mL)	Drug amount in the urine (mg)	Δt (hr) $t_2 - t_1$
0-1	200	0.200	40	1
1-2	50	0.400	20	1
2-3	50	0.200	10	1
3-4	100	0.050	5	1
4-5	25	0.100	2.5	1
5-6	125	0.010	1.25	1
6-12	250	0.005	1.25	6

Cont,

The rate method:

3- Calculate the rate of urinary excretion $\left(\frac{\Delta X_u}{\Delta t} \right)$

Time interval (h)	Volume (mL)	Concentration (mg/mL)	Drug amount in the urine (mg)	Δt (hr)	$\left(\frac{\Delta X_u}{\Delta t} \right)$ (mg/hr)
0-1	200	0.200	40	1-0=1	40
1-2	50	0.400	20	2-1=1	20
2-3	50	0.200	10	1	10
3-4	100	0.050	5	1	5
4-5	25	0.100	2.5	1	2.5
5-6	125	0.010	1.25	1	1.25
6-12	250	0.005	1.25	6	0.21

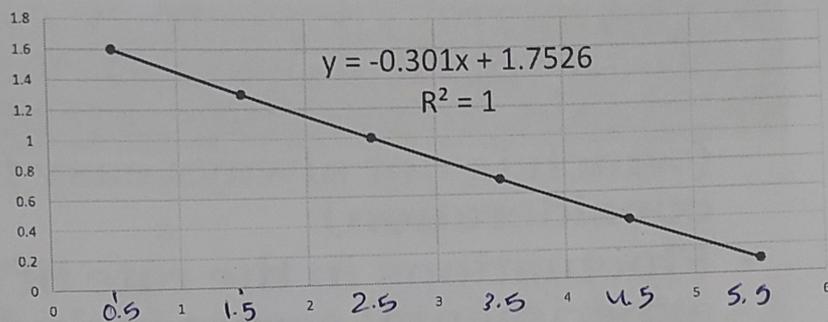
معدل تفرغ الأيون
 كالتالي: $\frac{\Delta X_u}{\Delta t}$

cont,

The rate method:

4- Plot time (mid of interval) vs. $\log(\Delta X_u/dt)$

Time (h)	$\left(\frac{\Delta X_u}{\Delta t}\right)$ (mg/hr)
0.5	40
1.5	20
2.5	10
3.5	5
4.5	2.5
5.5	1.25
9	0.21



بدرج الصغرى
x axis.

$$\log \frac{\Delta X_u}{\Delta t} = \underbrace{\log K_u X_0}_{\text{Intercept}} - \underbrace{\frac{Kt}{2.303}}_{\text{Slope}}$$

$$y = -0.301x + 1.7526$$

$$\log \frac{\Delta X_u}{\Delta t} = \frac{-kt}{2.303} + \log K_u X_0$$

Cont,

The rate method:

5- Estimate PK parameters from the values of the slope and the intercept

$$\text{Slope} = -\frac{K}{2.303} = -0.301$$

$$\Rightarrow K = 0.301 * 2.303 = 0.693 \text{ hr}^{-1}$$

$$\text{Intercept} = \log K_u X_0 = 1.7526$$

Signa minus method :- نفيها

$$\Rightarrow K_u = \frac{1}{X_0} \cdot 10^{\text{Intercept}} = \frac{1}{120} \cdot 10^{1.7526} = 0.471 \text{ hr}^{-1}$$

صالح
0.462 hr⁻¹

لأنه القيمة المتوقعة (مسألة توقع) لها بالطريقة الأولى هي مسألة estimation
Over (مسألة توقع) لأن القيمة المتوقعة (مسألة توقع) لها بالطريقة الأولى هي مسألة estimation