رح يطلب الدكتور نحسب ٣ شغلات بس على هاد الشابتر : K / Ku / Fraction

Intravenous Bolus Administration: Monitoring Drug in Urine

Not blood (plasma)

PK theory-
lec.6

Introduction

Pharmacokinetic parameters such as the elimination rate constant k may be calculated from urinary excretion data.

The following points should be noted.

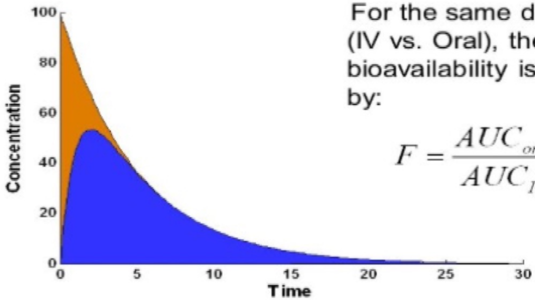
مش غزة ابرة

1) Urine collection is a non-invasive technique.
2) It is, perhaps, a more convenient method of sample collection, and sample size is generally not a problem. The sampling time, however, reflects drug in urine collected over a period of time, rather than a drug concentration at a discrete time. time intervales not specific times
3) Urinary data allow direct measurement of bioavailability, both absolute and relative, without the need of fitting the data to a mathematical model.

Bioavailability

Absolute Bioavailability	Vs.	Relative Bioavailability
It is determined for the same drug in various formulations. Example - Comparative study of bioavailability of a drug given through oral route and IV route.		It is determined for the various drugs. Example - Generic formulation is compared with a standard formulation of same drug in same dosage form.

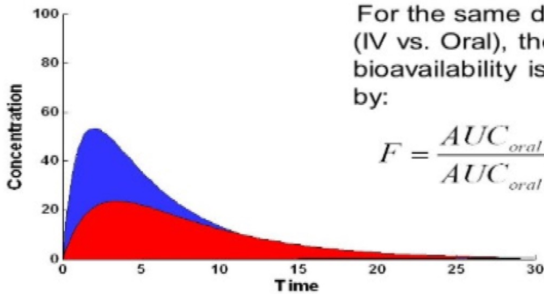
Absolute bioavailability



For the same dose (IV vs. Oral), the bioavailability is given by:

$$F = \frac{AUC_{oral}}{AUC_{IV}}$$

Relative bioavailability



For the same dose (IV vs. Oral), the bioavailability is given by:

$$F = \frac{AUC_{oral}(A)}{AUC_{oral}(B)}$$

min 1:11:17

Criteria for obtaining valid urinary excretion data:

- A significant amount of drug must be excreted unchanged in the urine (at least 10%).
- The analytical method must be specific for the unchanged drug; metabolites should not interfere. تعارون

جهازي لازم يتفرقه

- Water-loading should be done by taking 400 ml of water after fasting overnight, to promote diuresis and enable collection of sufficient urine samples.
- Before administration of drug, the bladder must be emptied completely after 1 hour from water loading and the urine sample taken as blank; the drug should be then administered with 200 ml of water and should be followed by 200 ml of given at hourly intervals for the next 4 hours.
- Volunteers must be instructed to completely empty their bladder while collecting urine samples.
- Frequent sampling should be done in order to obtain a good curve.
- During sampling, the exact time and volume of urine excreted should be noted.
- An individual collection period should not exceed one biological half-life of the drug and ideally should be considerably less.
- Urine samples must be collected for at least 7 biological half-lives in order to ensure collection of more than 99% of excreted drug. 7h * HL(h) = فترة جمع البول من المريض
- Changes in urine Ph and urine volume may alter the urinary excretion rate.

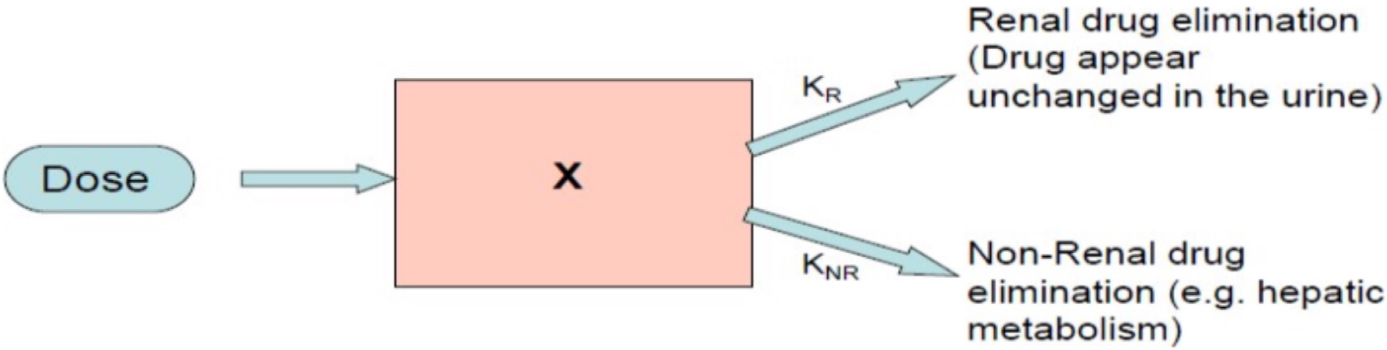
① 400 ml water after fasing

② complete emptying of the bladder. sample = blank

③ drug + 200 ml water with 200 ml / 1h for 4h (Tot = 800 ml)

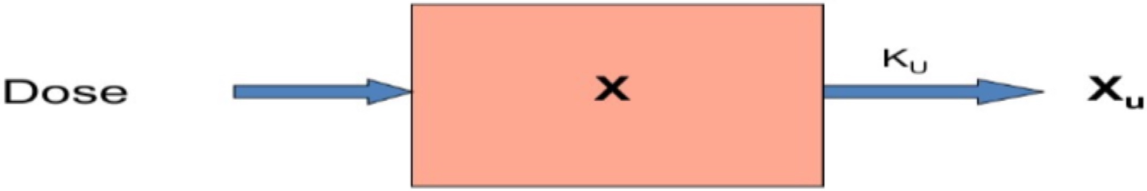
④ every time you feel like urination do it immediatly and completly

Renal and Non-renal elimination pathways



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

K non-renal = zero



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

Methods to compute PK parameters from urinary data

الاكثر دقه

1. the "amount remaining to be excreted'' method (ARE); also known as the sigma- minus method

2. The rate of excretion method.

Sigma-Minus Method

- Amount of unchanged or excreted drug in urine (X_u) is given by:

Amount of the drug in urin at specific time

$$Xu = \frac{\overset{\text{Krenal}}{Ku}\overset{\text{dose}}{Xo}}{K_{\text{Tot}}}\underbrace{(1-e^{-Kt})}_{\text{Remaining to be execreated}} = \overset{\text{cumilative amount of drug}}{X_u^{\infty}}(1-e^{-Kt})$$

$X_u^{\infty} = X_o$ when:
$Ku = K$ drug exereated exclusivly in urin.

where K is the elimination rate constant, K_u or sometimes referred to as K_r is the renal elimination (or excretion) constant and X_o is the dose, X_u^{∞} is the cumulative amount of drug excreted in the urine at t $= \infty$

$* \text{ At } t=0 \longrightarrow X_u = \text{zero}$

$* \text{ At } t=\infty \longrightarrow t=7 \longrightarrow X_u^{\infty} = \frac{K_u X_o}{K}$

Sigma-Minus Method

1

- At $t = 0$; $e^{-k^*t} = 1$

then $X_U{}^o$= Dose [1 - 1] = 0

- At $t = \infty$; $e^{-k^*t} = 0$ ➔ $\boxed{X_u^{\infty} = \frac{KuXo}{K}}$

Re-aranging the above equation yields:

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

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

Cont,

When all the drug is eliminated unchanged in the urine then $X_U^{\infty} = X_o$

$$(Xu)_t = Xo * (1 - e^{-Kt})$$

Where K=Ku

Cont,

Sigma-Minus Method

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

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

$$Xu^{\infty} - Xu = Xu^{\infty} e^{-kt}$$

$$\boxed{\underbrace{\log(Xu^{\infty} - Xu)}_{Y} = \underbrace{\log Xu^{\infty}}_{mx} - \frac{Kt}{2.303}}$$

Y = mx − c

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

Remember when the drug is excreted 100% renally then Ku=K and Xu=Xo; otherwise $Xu^{\infty} = \frac{X_0 * K_u}{K}$

Sigma-Minus Method (Example)

$X_0 \neq X_0^{\infty}$

- 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.

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

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

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^∞

120

80 → Renal

40 → non-renal (مابعرف)

3- Calculate amount remaining to excreted (ARE)

C*V

Cumulative Xu

Xu

Time interval (h)	Volume (mL)	Concentration (mg/mL)	Drug amount in the urine (mg)	Cumulative amount in the urine (mg)	ARE $(Xu^\infty - Xu)$ (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

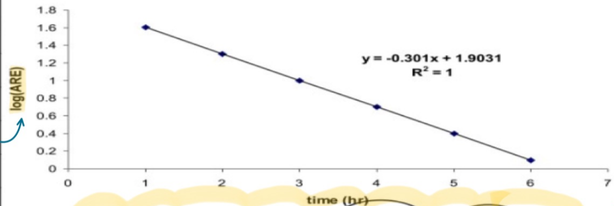
80

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

بهاي الـmethod باخذ الاخير

Time interval (h)
0-1
1-2
2-3
3-4
4-5
5-6
6-12

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



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

Intercept

Slope

هيك بتيجي بالامتحان جاهزه

فهم بس مش رح ييجي

Cont,

Sigma-Minus Method :

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

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

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

Intercept = $\log Xu^{\infty}$ = 1.9031

Xu∞ = 80 mg

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

80 = (Ku * 120) / 0.693

Ku = 0.462 hr-1

توضيح

$$\underbrace{\log(Xu^{\infty} - Xu)}_{} = \underbrace{\log Xu^{\infty}}_{\text{intercept}} - \underbrace{\frac{Kt}{2.303}}_{\text{slope}}$$

y = -0.301x + 1.9031

① $-0.301 = -\frac{K}{2.303}$

$K = 0.693\ hr^{-1}$

② Find ku :

$X_u^{\infty} = \frac{kuXo}{K} \Rightarrow 80 = \frac{120ku}{0.693} \rightarrow ku = 0.462$

k renal

$\log X_u^{\infty} = 1.9031$

$X_u^{\infty} = 80\ mg$

③ K non-renal

$K = k_R + k_{non\text{-}R} \rightarrow 0.693 = 0.462 - k_{non}$

$K_{non} = 0.231$

Knr ??? 0.231 hr-1

Cont,

Limitations of the Sigma-Minus Method

1. Urine samples must be collected until such time that, practically, no additional drug appears in the urine (i.e.5-7 half-life) long HLs req collection urin for a long period of time
2. No urine samples can be lost, or urine from any samples used in the determination of Xu (the exact volume of urine at each time interval must be known) → Nothing lost not even 1ml
3. This is a time-consuming method for a drug with a long elimination half life (t1/2)
4. There is a cumulative build up of error → أخطاء حسابية ورياضية

Rate method

The rate method

A
C / time

- The rate of urinary excretion $\left(\frac{\Delta Xu}{\Delta t}\right)$ is given by:

$$\frac{\Delta Xu}{\Delta t} = K_u \cdot X = Ku \cdot Xo \cdot e^{-Kt}$$

- Previous equation can be represented as:

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

we can find K / Ku eaiser here (same equ.)

The rate 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.

The rate method (Example)

نفس السؤال

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مش مطلوبين
للمره الثانيه

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

2- Calculate the change in time

Time interval (h)	Volume (mL)	Concentration (mg/mL)	Drug amount in the urine (mg)	Δt (hr)
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

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

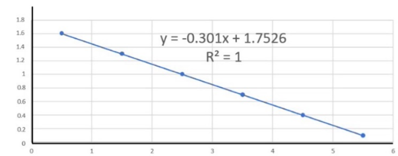
ΔXu / Δt =

Time interval (h)	Volume (mL)	Concentration (mg/mL)	Drug amount in the urine (mg)	Δt (hr)	$\left(\frac{\Delta Xu}{\Delta t}\right)$ (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

4- Plot time (mid of interval) vs. log(dXu/dt)

نقطة منتصف

Time (h)	$\left(\frac{\Delta Xu}{\Delta t}\right)$ (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



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

Intercept

Slope

① slop = $-\frac{K}{2.303}$ = -0.301

$K = 0.301\ (2.303)$

$K = 0.693\ hr^{-1}$

② intercept :

$\log KuXo = 1.7526$

$KuXo = 10^{(1.7526)}$

$KuXo = 56.5718$

∴ $Ku = \frac{56.5718}{120}$ → $Ku = 0.471\ hr^{-1}$ (overestimating)

K

اختلاف بسيط مع الطريقة الاولى

($ku = 0.462$)

③ K non-renal

$K = k_R + k_{non\text{-}R}$ → $0.693 = 0.471 - k_{non}$

$K_{non} = 0.222$

Cont,

The rate method:

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

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

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

$$Intercept = \log KuXo = 1.7526$$

KuX0 = 101.7526

= 56.5718

Ku = 56.5718/ 120 = 0.471 hr-1

Knr = ?0.222 hr-1

Cont,

General comment on rate method

Ku

- The method tends to give overestimate of intercept. The overestimation can be minimized by collecting urine samples more frequently (which is not always easy from practical consideration)
- Fluctuations in the rate of drug elimination and experimental errors including incomplete bladder emptying for a collection period cause appreciable departure from linearity using the rate method, whereas the accuracy of the sigma-minus method is less affected

Practice question 1

segma - method

The following cumulative amounts of the drug in the urine were obtained after intravenous bolus injection of 500 mg of the drug which is exclusively eliminated by urinary excretion. **Determine the following using the rate method:**

Ao

→ $A_0 = A_\infty$

① حولها الى:

② احسب هاي باد rate

ما دح يجي هيك فكرة

a) The elimination half-life

b) The cumulative amount of the drug eliminated on the urine following 7 hrs following 500 mg dose

③ ارجع احسب ال A بعد 7 ساعات بالسيغما

ما بيجي جدول بالامتحان

Time (h)	Xu (Cumulative) (mg)
2	190
4	325
6	385
8	433
10	460
12	474

t=7

Time (h)	Cumulative Xu (mg)	Xu	dt	Dxu/dt	T (mid) (hr)
2 (0-2)	190	190	2	95	1
4 (2-4)	325	325-190=135	2	67.5	3
6 (4-6)	385	60	2	30	5
8 (6-8)	433	48	2	24	7
10 (8-10)	460	27	2	13.5	9
12 (10-12)	474	14	2	7	11

Cont

$$Xu = \frac{\cancel{Ku}Xo}{\cancel{K}}(1-e^{-Kt}) = X_u^{\infty}(1-e^{-Kt})$$

$Ku = K$

$Xu_{(t=7)} = Xo\,(1-e^{-Kt})$

$Xu = 500\,(1-e^{-(0.26)(7)})$

$Xu = 418.9 \approx 420$ mg

جواب الدكتور

$385 < 420 < 433$

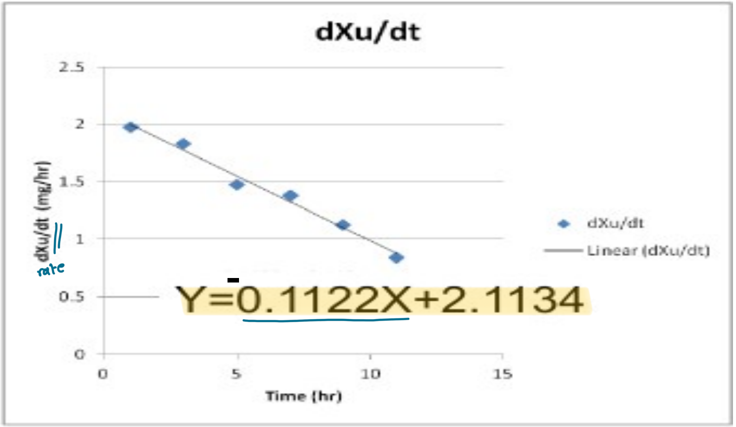
Practice question 1

- -K=2.303*slope
- K=0.26 hr^{-1} ✓

a) Half life= 2.7 hrs $\frac{0.693}{K}$

b) The cumulative amount of the drug eliminated in the urine following 7 hrs following 500 mg dose

Ao
Xo



$$(Xu)_t = Xo * (1 - e^{-Kt})$$

Xu at 7 hrs =420 mg

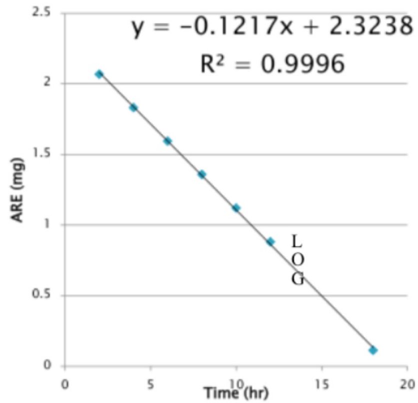
$$\log\frac{\Delta Xu}{\Delta t} = \log KuXo - \frac{Kt}{2.303}$$

$\frac{K}{2.303} = 0.1122 \rightarrow K = 0.258$

Practice question 2

- Utilizing urinary data (sigma minus method), the following curve was obtained was obtained for an antibiotic. Calculate the fraction of the drug excreted unchanged in the urine assuming that the patient received 500 mg of the antibiotic.

Ao



$$①\ \frac{X_u^\infty}{\checkmark X_o} = \frac{③\ Ku}{②\ K} = fe$$ — our formela

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

$$y = 2.3238 - 0.1217x$$

الحل

① $\log Xu^\infty = 2.3238$

$Xu^\infty = 210.7657 \approx 210.3778$ رقم الدكتور

$fe = \frac{210.3778}{500} = 0.4207$

$\therefore \% fe = 42.1\%$ of drug is excreted unchanged in orin

اشياء اضافيه

② $K = 0.1217(2.303) = 0.28$

③ $Ku = \frac{Xu^\infty}{Xo} * K = \frac{210.3778}{500} * 0.28 = 0.1178\ hr^{-1}$

$Intercept = \log Xu^\infty$ =2.3238

so $X_u^\infty = 10^{2.3238}$

$X_u^\infty = 210.3778$

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

fe=210.3778/500=0.4207*100=42.1%

So how much was Fm or fraction of drug metabolized?

K = 2.303 * 0.1217

= 0.28 hr -1

Xu∞ = Ku * X0/ K

210.3778 = Ku * 500/ 0.28

Ku = 0.1178 hr-1

fe = Ku/ K

= 0.1178 / 0.28

= 0.42

= 42%