MIRACLE Academy

حركية الدواء

لجان الدُفعات

Intravenous Bolus Administration: Monitoring Drug in Urine

PK theory-lec.6

بدنا

دايماً عينات عن urine sample مش ب blood

Introduction

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

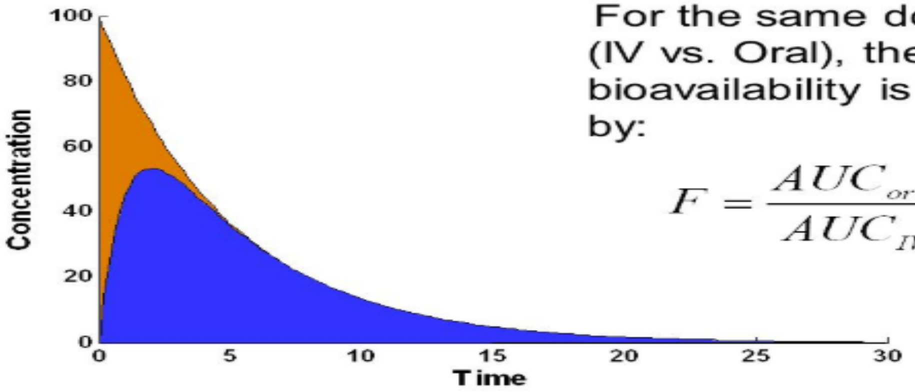
The following points should be noted.

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.
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.

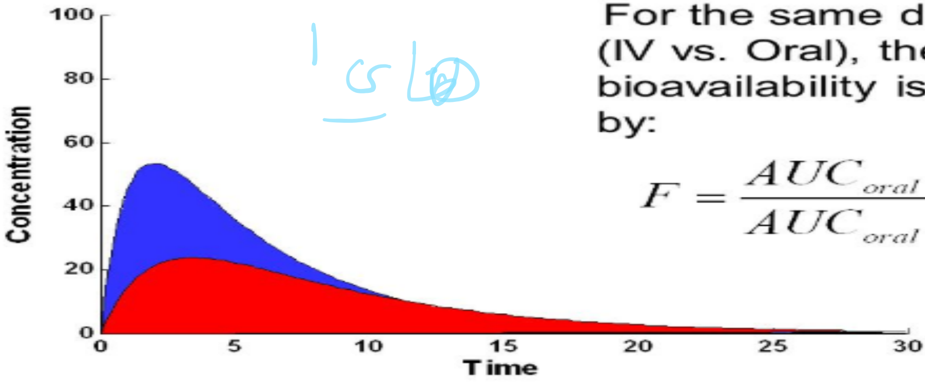
Absolute bioavailability



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

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

Relative bioavailability



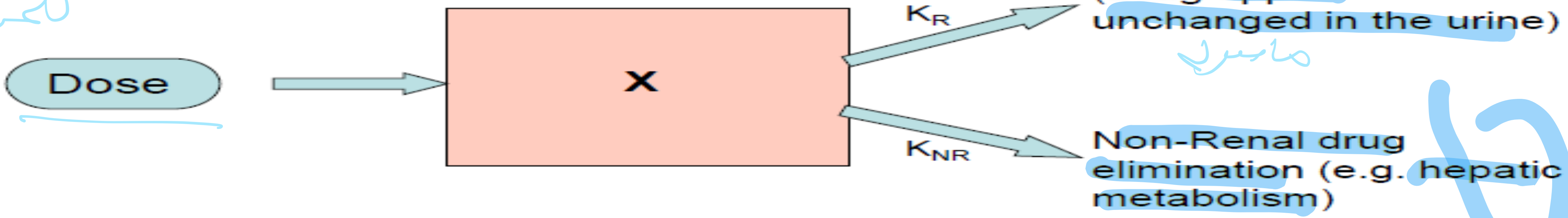
For the same dose (IV vs. Oral), the bioavailability is given by:

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

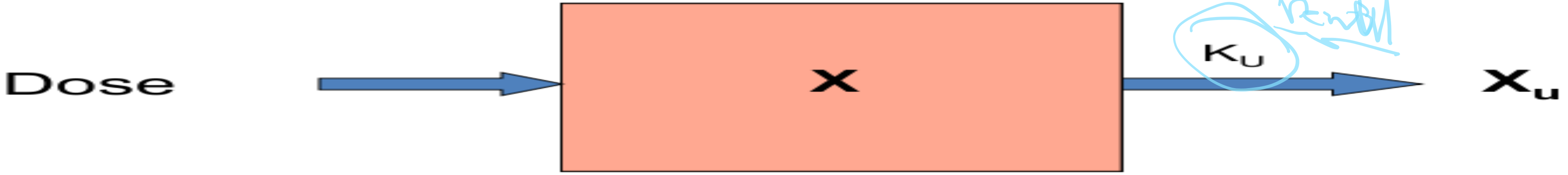
Criteria for obtaining valid urinary excretion data:

- 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.
- 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.
- Changes in urine Ph and urine volume may alter the urinary excretion rate.

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)

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

Methods to compute PK parameters from urinary data

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:

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

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 = ∞

Sigma-Minus Method

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

then X_U^o = Dose [1 - 1] = 0

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

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,

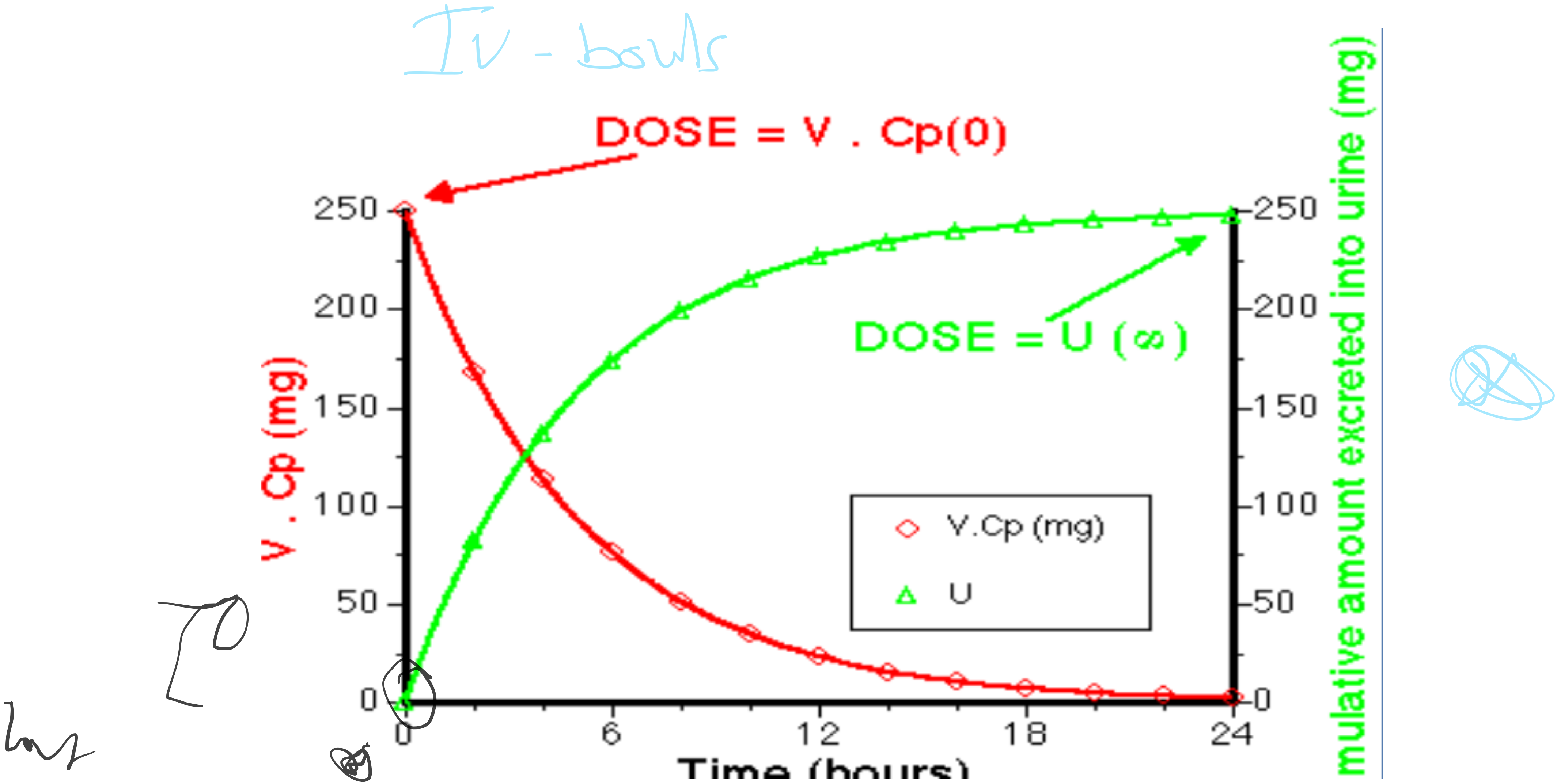
كله الدواء حكالك إذا
$K_u = K$ إذا eliminated صار صحيح

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

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



Cont,

Sigma-Minus Method

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

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

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

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

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

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

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.

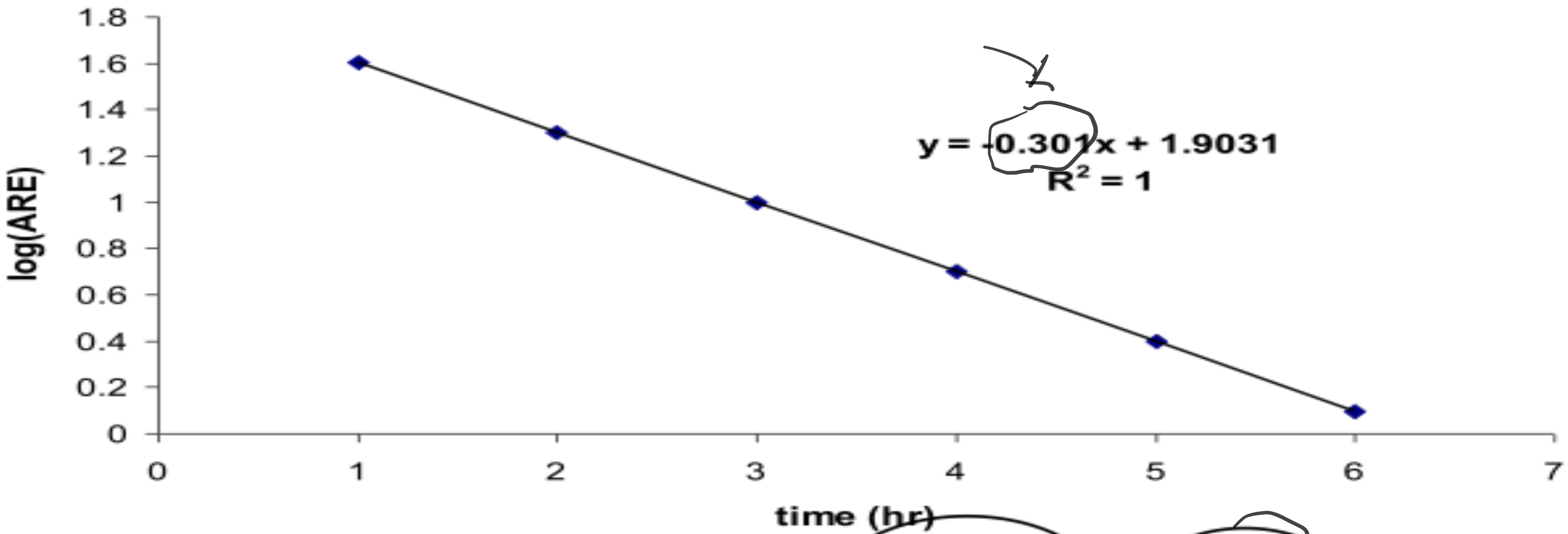
- The following Table provides the urinary data in a tabulated form.

Cont,

Sigma-Minus Method :

Amount remaining to be eliminated (ARE)

$(Xu^{\infty} - Xu)$



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

Intercept

Slope

Cont,

Sigma-Minus Method (Example)

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,

Sigma-Minus 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

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^{∞}

Cont,

Sigma-Minus Method :

3- Calculate amount remaining to excreted (ARE)

C*V

Cumulative Xu

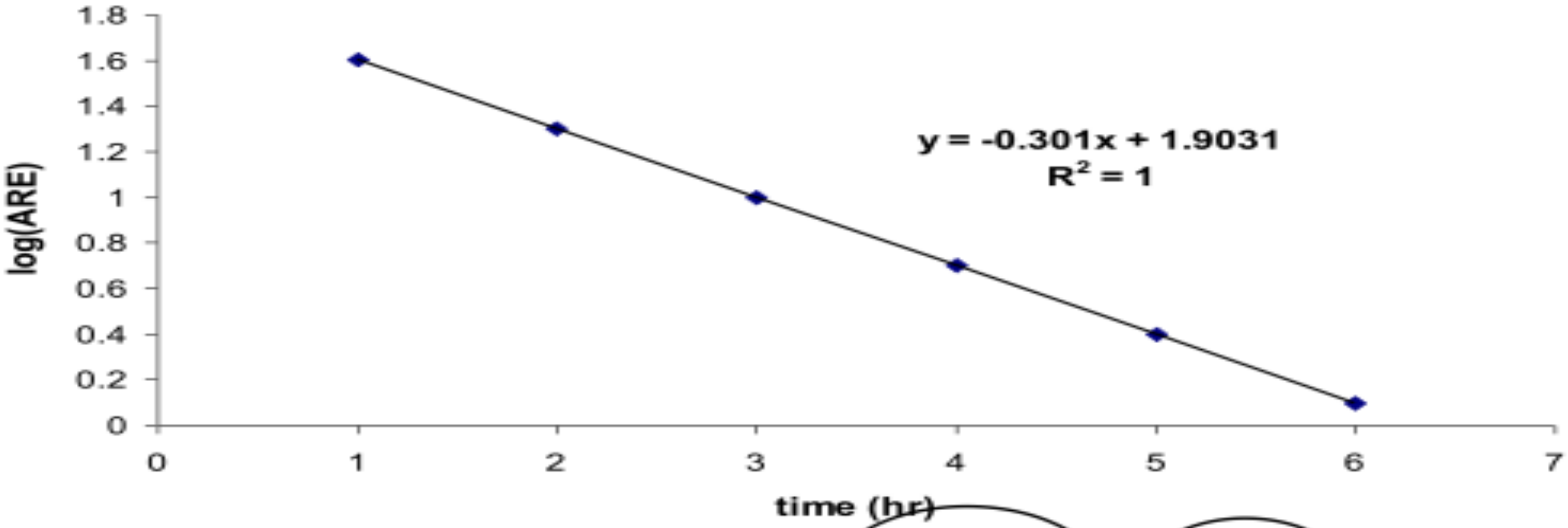
Time interval (h)	Volume (mL)	Concentration (mg/mL)	Drug amount in the urine (mg)	Cumulative amount in the urine (mg)	ARE $(Xu^{\infty} - Xu)$ (mg)
0-1	200	0.200	40	40	40
1-2	50	0.400	20	60	20
2-3	50	0.200	10	70	10
3-4	100	0.050	5	75	5
4-5	25	0.100	2.5	77.5	2.5
5-6	125	0.010	1.25	78.75	1.25
6-12	250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

Cont,

Sigma-Minus Method :

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

Time (h)	ARE $\left(Xu^{\infty} - Xu\right)$ (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: $\log Xu^{\infty}$

Slope: $-\frac{K}{2.303}$

Cont,

Sigma-Minus Method :

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

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

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

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

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

How about Knr?

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)
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)
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

Rate method

The rate method

- 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:

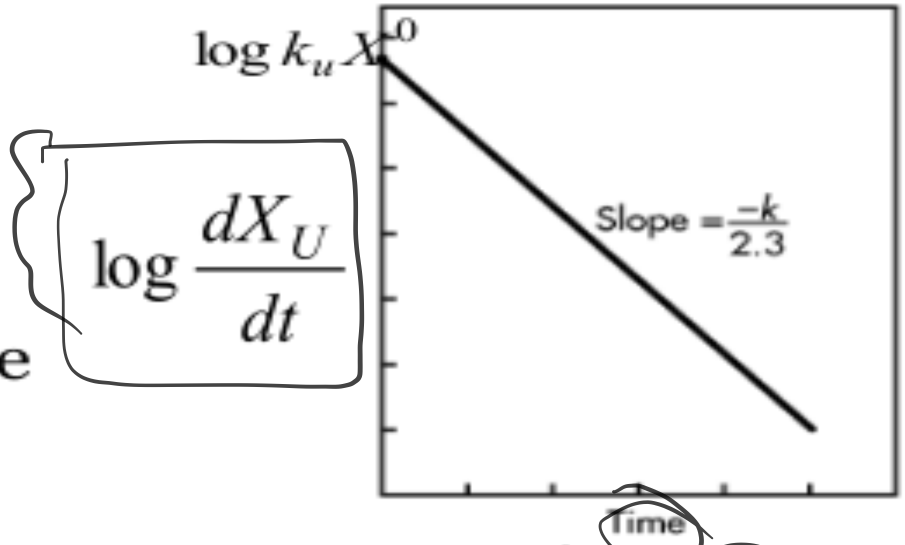
$$\log \frac{\Delta Xu}{\Delta t} = \log KuXo - \frac{Kt}{2.303}$$

Cont,

The rate method

A straight line is obtained by plotting the previous equation

Therefore, if X^o 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)

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- 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
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,

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

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)
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

y-axis

log dXu / Δt

Cont,

The rate method:

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

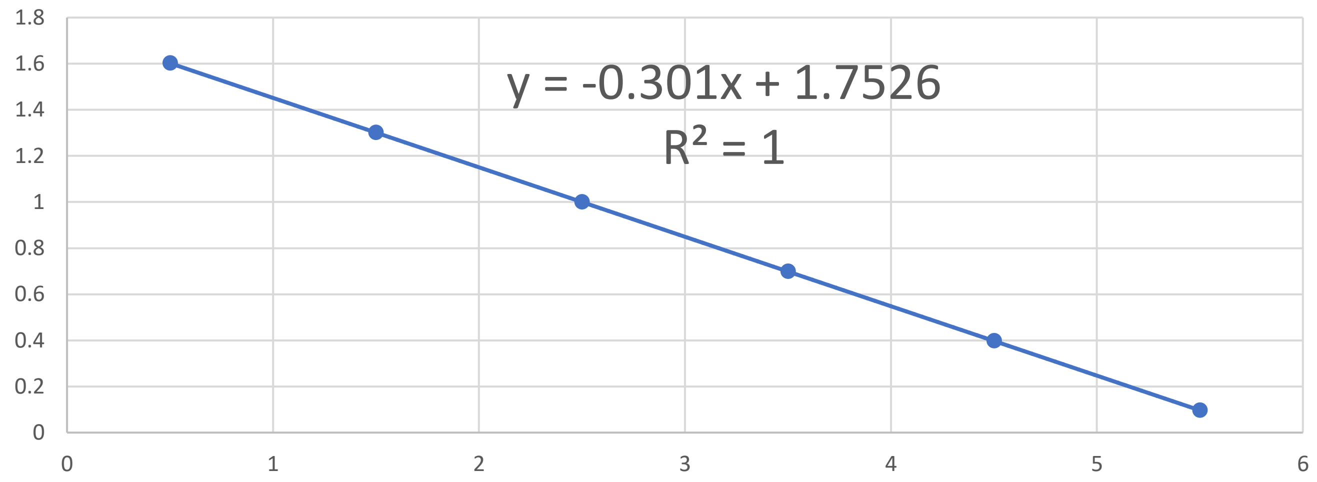
Time interval (h)	Volume (mL)	Concentration (mg/mL)	Drug amount in the urine (mg)	Δt (hr)	$\left(\frac{\Delta Xu}{\Delta t}\right)$ (mg/hr)
0-1	200	0.200	40	1-0=1	40
1-2	50	0.400	20	2-1=1	20
2-3	50	0.200	10	1	10
3-4	100	0.050	5	1	5
4-5	25	0.100	2.5	1	2.5
5-6	125	0.010	1.25	1	1.25
6-12	250	0.005	1.25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

cont,

The rate method:

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

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: $\log KuXo$

Slope: $\frac{K}{2.303}$

Cont,

The rate method:

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

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

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

$$Intercept = \log KuXo = 1.7526$$

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

Cont,

General comment on rate method

- 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

example

Practice question 1

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:**

a) The elimination half-life
b) The cumulative amount of the drug eliminated on the urine following 7 hrs following 500 mg dose

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

Cont,

Practice question 1

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

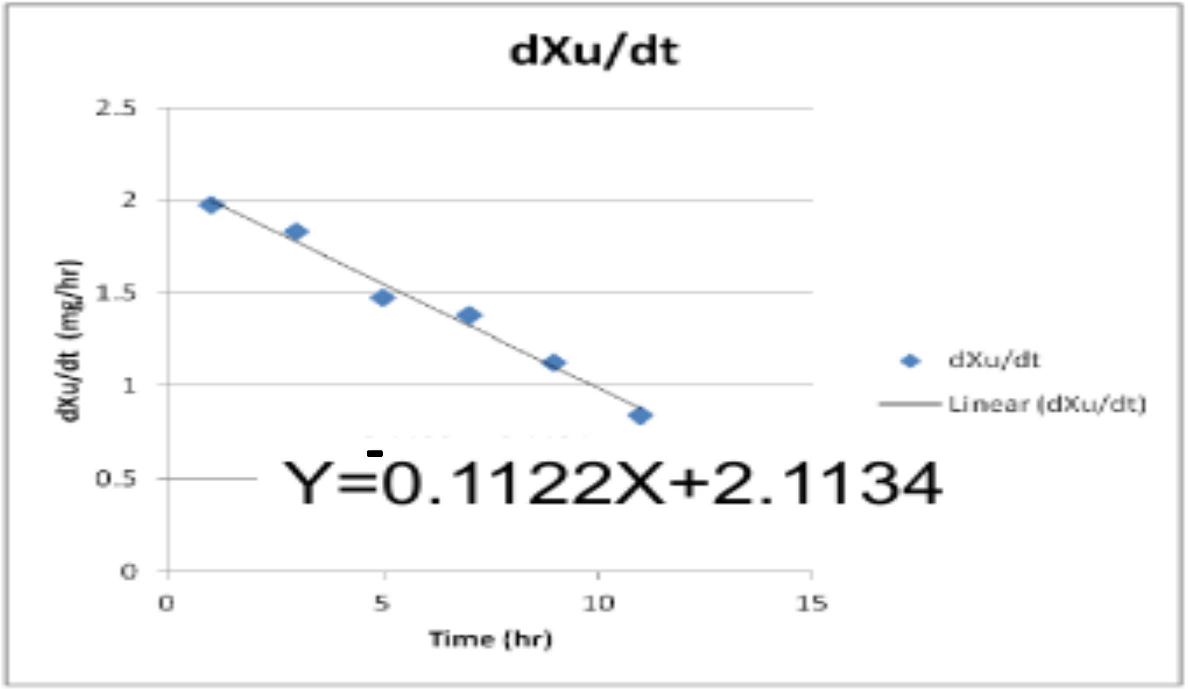
Cont,

Practice question 1

- -K=2.303*slope
- $K=0.26\ hr^{-1}$

a) Half life= 2.7 hrs

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



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

Xu at 7 hrs =420 mg

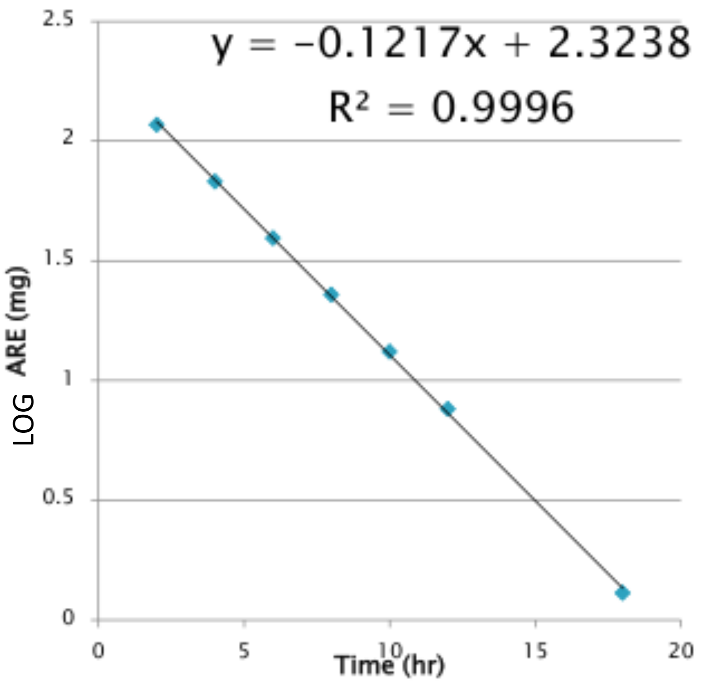
Cont,

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.

Cont,

Practice question 2



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

so X_u^{∞}=$10^{2.3238}$

X_u^{∞}=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?