Pharmacokinetics

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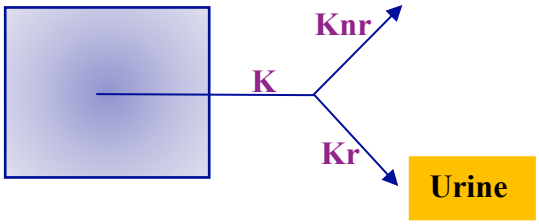
Evaluation of Drug Kinetics By the Utilization of Urinary Excretion Data (One comp IV-Bolus)

- We talked about IV bolus where we tested plasma concentration versus time, now we will be dealing with **urine** instead of plasma.
- Remember: we have talked about clearance which has an additive characteristic so we can add the clearance by different organs together to get the total-body clearance.

- **Clearance** may be applied to any organ that is involved in drug elimination from the body. As long as first-order elimination processes are involved, clearance represents the sum of the clearances for each drug-eliminating organ.



- **Notes:**
  - We also divided clearance into renal clearance (through the kidney) and non-renal clearance.
  - We evaluate the renal clearance for each drug this helps in dose adjustment in case of renal failure or kidney dysfunction Especially for drugs that are illuminated by the kidney and those that have a narrow therapeutic window.
  - We evaluate the elimination of drugs through the renal system by collecting urine and determining the fraction of the drug that is eliminated by the renal system.

- **Plasma data VS urine data:**
  - In **testing plasma data** we used a cannula in the patient's arm and we determined the exact time that we would test the concentration on. Then we plot concentration VS time and obtain our data.
  - While **testing urine**, can we take samples Instantaneously? No, We can't collect concentration at any time we want (because urine is collected in the bladder then all of it is excreted) instead we take intervals and calculate the volume and concentration.

- **Concentrations?**
  - Can we use the concentration of the drug in urine to represent the elimination process or not? if we have two samples with different concentrations, the first sample has a concentration of 4 mg/L and the second one has a concentration of 3 mg/L.

    Can we assume that the first sample actually has a higher amount of a drug than the second one like we did in testing plasma concentration? No, We can't do that because the **volume** in each interval is different than the other! Urine volume is **not constant** like it used to be when we tested plasma.

    Different volume means different AMOUNT, as an example:
    The **first sample** 4 mg/L was in 50 ml => Amount = 200 mg
    The **second sample** 3 mg/L was in 200 ml => Amount = 600 mg

If we tested the sample with 3 mg/L has a higher amount of drug because it has a different volume.

- So, In the case of urinary data, we don't deal with the concentration of drugs in urine, instead, we have to convert concentration into amount this is because the volume is not constant.
- Remember: amount = conc*volume

In the case of plasma data, higher drug concentration was enough to determine a higher amount because the volume of the sample was constant.

Plasma	Urine
Time	Time intervals
Conc	Amount

$$\frac{dXu}{dt} = KrX$$

- **dXu/dt:** the rate of drug appearance in urine. **X:** amount of the drug in the body.
- We administer the drug intravenously with a certain dose Xo, at first the amount of drug in the blood will be high then it will start decreasing with time, but the rate of a drug appearance in urine will increase with time.

Notice here that we said the rate of appearance which indicates increasing of the drug amount with time. The rate of drug appearance (dXu / dt) is increasing = the slope is positive.

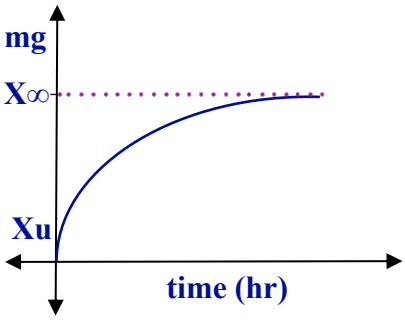
- **Now let's start evaluating the drug kinetics using urinary data:**
  - Execration through the kidney is a first-order process (one compartment).
  - In order to obtain urinary data of certain drugs; at least a part of the dose should be eliminated through renal system.
  - Renal elimination = execration = the drug is removed unchanged in the urine.

$$K_{total} = Kr + Knr$$

Kr : Renal elimination rate constant.

Knr: Non-renal elimination rate constant.

- **Since we are dealing with amounts:**
  - We have the amount of a drug in the body (dose we give): **Xo**
  - And we have the total amount of drug excreted in urine (We calculate It by adding all amounts of a drug excreted in the urine): **Xu∞**
  - Using these amounts we can calculate the fraction of drug execrated unchanged in urine = (**Xu∞ / Xo**).
  - Also : **(Kr / K) = (Xu∞/Xo)** the same! Both meant the same fraction.
  - Urine is a closed system (not like the plasma open model) because there is no loss of the drug (the amount of drug in urine stays in the urine).



Xu: amount of drug in urine.

Xu∞: the total amount of drug excreted unchanged in urine.

At time zero: no drug in urine so Xu= 0
With time Xu Increases until a certain time it will be constant because there will be no drug to be execrated in the urine, this constant value is called the total eliminated amount in urine Xu∞

Xu is a Cumulative value:
At 1st hr: 100 mg
At 2nd hr: 150 mg
At 3rd hr: 175 mg

- **How to evaluate the drug Pharmacokinetics using urinary data?**
  - Emptying of the bladder: the volunteer needs to empty their bladder so no dilution of the dose can occur.
  - Dosing: giving the volunteer the drug dose through IV bolus (at zero time = administration time).
  - Collecting urine over time intervals: we collect all the urine in the whole interval (even if the person went to the bathroom many times during one interval, we collect all the samples that had been taken during the interval).
    At the end of each interval, we must empty the bladder again .
  - Calculating the amount of the drug in urine: by multiplying volume and concentration:
    Amount = volume*concentration

- **We deal with urinary data by two methods:**
  - Rate method. (Plot Rate Vs Time).
  - Sigma minus method. (Plot Amount remaining to be excreted Vs time).

Rate method

- Renal excretion is a **first order** process, so it has a constant Kr renal elimination rate constant, so the rate of drug appearance in urine =

$$\frac{dXu}{dt} = \mathbf{KrX}$$

Kr: renal Elimination rate constant

X: amount of the drug in the body (not urine)

- The **rate** of drug elimination depends on the **amount** of drug in the **body** **Xo**.
- The **more a drug** is present in the body, the **higher its elimination rate**. Over time, the drug concentration in the body will **decrease**, resulting in a **lower elimination rate**. (Note: We discussed this in the context of the body, not the urine.)

- **Equations:**

$\frac{dXu}{dt}$ = KrX (X=Xoe $^{-kt}$)

$\frac{dXu}{dt}$ = Kr Xoe $^{-kt}$ **Exponential Form**

$\log\frac{dXu}{dt} = \log(KrXo) - \frac{K}{2.303}t$ **Logarithmic Form**

$\ln\frac{dXu}{dt} = \ln(KrXo) - Kt$ **Ln Form**

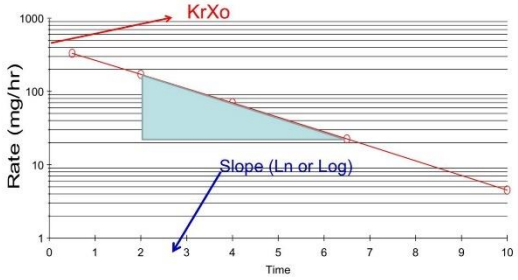
- If we plot the rate (dXu/dt) Vs time (t) on a semi log paper we will get a linear relationship

Y-intercept: KrXo

Slope = -k (exponential)

= -k → (ln)

= -k/2.303 → (log)



- A quick note regarding the equation: we initially expressed the rate as (dXu/dt), which is instantaneous. However, this isn't practical with urine since, as we discussed, I can't take a sample at any given moment; I have to wait for the bladder to empty. Therefore, we replace the instantaneous expression with the average rate (ΔXu/Δt).

$\log\frac{dXu}{dt} = \log(KrXo) - \frac{K}{2.303}t$ => $\mathbf{\log\frac{\Delta Xu}{\Delta t} = \log(KrXo) - \frac{K}{2.303}t}$

$\ln\frac{dXu}{dt} = \ln(KrXo) - Kt$ => $\mathbf{\ln\frac{\Delta Xu}{\Delta t} = \ln(KrXo) - Kt}$

- **Example**: After administration of 1000 mg of cefazolin, urine samples were collected and the following data were obtained:

Time interval	Volume (ml)	Conc (mg/ml)
0-1	65	5.1
1-3	114	3.0
3-5	140	1.0
5-8	225	0.3
8-12	180	0.1

- To follow the rate method, we need to find ΔXu, Δt, and T. The remaining parameters will be obtained from the plot.
- Steps:
  - ✓ Calculate the **amount** for each interval:
    - Multiply the concentration by the volume to get the amount: Amount= ΔXu
    - Note: This is not the same as Xu (which is cumulative).
    - Xu represents the total amount excreted (including all prior amounts), so if we have Xu, we must subtract the previous value to get ΔXu for the current interval.
      - ☑ If we have ΔXu, no further adjustments are needed.
      - ☑ If we only have Xu, calculate ΔXu by subtracting the previous value from the current on.

  - ✓ Calculate **Δt** for each interval: Δt = Upper limit - Lower limit

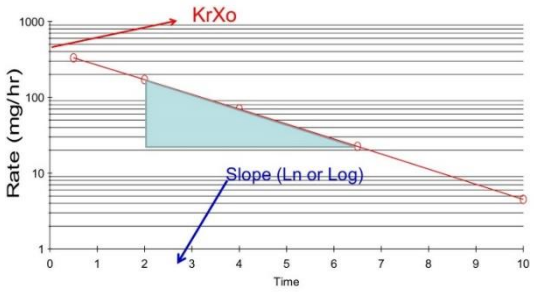
  - ✓ Calculate the **average rate**:
    For each interval, calculate the rate as: Average rate = ΔXu/Δt
    Plot the rate averages (ΔXu / Δt) on the Y-axis.

  - ✓ Determine the **time** to plot on the **X-axis**:
    Since the time is an interval, we plot T-mid (the midpoint of the interval) on the X-axis.
    T-mid = (Upper limit + Lower limit)/2
    Why choose the midpoint? Since we're calculating the average rate, the time value should also represent the middle of the interval.

    This method helps in plotting the **average rate** over **each interval** and accurately reflects the timing of drug elimination.

Time interval	Volume (ml)	Conc. (mg/ml)	Amount mg	Δt hr	ΔXu/ Δt mg/hr	T-mid hr
0-1	65	5.1	331.5	1	331.5	0.5
1-3	114	3.0	342	2	171	2
3-5	140	1.0	140	2	70	4
5-8	225	0.3	67.5	3	22.5	6.5
8-12	180	0.1	18	4	4.5	10

- Now we are ready to plot the **average rate Vs T-mid** and on a semi-log paper we get a linear relation:
  - ✓ Y-intercept = Kr Xo = 410 mg/hr
  - ✓ If **Xo** = 1000 mg then **Kr** = 0.41 hr^{-1}
  - ✓ **K:** from the slope of two points = 0.45 hr^{-1}
  - ✓ **Kr** : from y-intercept = 0.41 hr^{-1}
  - ✓ K = Kr + Knr
    0.45 = 0.41 + **Knr**
    Knr = 0.04 hr^{-1}



$K=0.45hr^{-1}$, $t_{0.5}=1.54$ hr,
$Kr=0.41hr^{-1}$, $Knr=0.04hr^{-1}$

- Kr is higher than Knr which means that this drug is mainly eliminated by renal system. The fraction of a drug eliminated by renal system (unchanged) is :
  (Kr / K) = 0.41/ 0.45 = 0.9 = almost **90% is eliminated through renal system**.

- **Note:** The reason the slope of the graph gave us K instead of Kr is that the graph represents the **rate**, which depends on the **amount of drug in the body**. The amount is controlled by all eliminations in the body, not just renal elimination.

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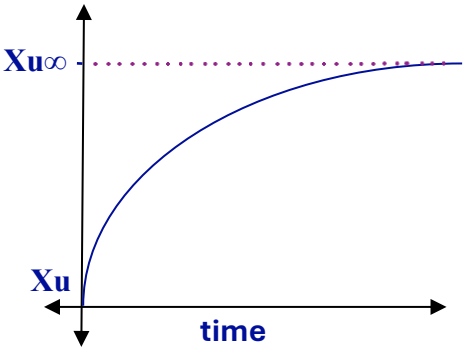
Sigma minus method

- The rate of elimination depends on the amount of the drug in urine Xu (not the body).



- The amount is increasing: the function is growth (1-e $^{-Kt}$)
  Xu = Xu∞ (1- e $^{-Kt}$)
- At **zero** time (t=0)
  Xu = Xu∞ (1- e ^{0})
  Xu = Xu∞ (1-1)
  Xu = Zero, This makes sense because at zero time there is no drug in the urine.
- At time **infinity** (t=∞)
  Xu = Xu∞ (1- e)
  Xu = Xu∞ (1-0)
  Xu = Xu ∞, This makes sense because we said that is the total amount of a drug in the urine.

- **Xu = Xu∞ (1- e $^{-Kt}$)**
  Xu =(Kr / K)*Xo (1- e $^{-Kt}$)

- Remember:
  (Xu∞/ Xu) =(Kr / K)
  So, Xu∞ = (Kr / K) * Xo
  What does that mean? the total amount of drug in urine Xu∞ is actually the fraction of a drug eliminated by the renal system Kr / K multiplied with the total amount in the body Xo

- **Equations:**

  $Xu = Xu\infty\ (1-e^{-Kt})$ => **Exponential Form**

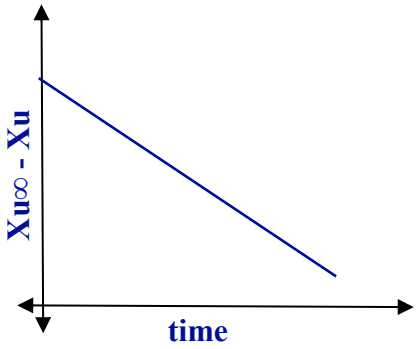
  $Xu = Xu\infty - Xu\infty\ e^{-Kt}$

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

  $Log(Xu\infty - Xu) = logXu\infty - \frac{K}{2.303}t$ => **Logarithmic Form**

  $ln(Xu\infty - Xu) = lnXu\infty - Kt$ => **Ln Form**

- **How to plot it?** on the **Y-axis : (Xu∞ - Xu),** on **X-axis: time** on a semi-log paper:



- Y-intercept : Xu ∞
- Slope: -k (exponential)
  -k (Ln)
  -k/2.303 (Log)

- Focus on Y-axis, what is (Xu∞ - Xu) ? Let's understand this with an example:
- If a drug is given in a dose of 500 mg , it will be eliminated through:
  - ✓ renal system Kr : for example 300 mg => Xu∞= 300 mg
  - ✓ Non renal system Knr: for example 200 m

Time interval	Xu
0-1	100
1-3	175
3-6	270
6-10	300

- At 1st time interval, the urine will have 100 mg of a drug
- According to (Xu∞ - Xu) = 300-100 = 200 mg
- 200 mg (is the amount remaining to be excreted/ ARE): the amount of drug in the body that will be eliminated by the Renal system.
- (In the first hour, the renal system took 100 units of the drug, and there are still 200 units remaining).

- **Note: we said the amount remaining to be excreted not eliminated, why?**
  "Excreted" specifically refers to the removal of the drug through the renal system (urine), while "eliminated" encompasses all mechanisms by which the body gets rid of the drug, including metabolism and other routes of excretion.

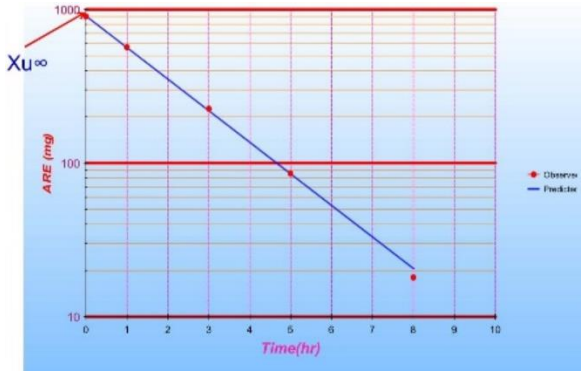
- So let's deal on plotting ARE on Y-axis:

Time interval	Volu (ml)	Conc (mg/ml)	Amount mg	Xu mg	ARE mg	T-end hr
0-1	65	5.1	331.5	331.5	567.5	1
1-3	114	3.0	342	673.5	225.5	3
3-5	140	1.0	140	813.5	85.5	5
5-8	225	0.3	67.5	881	18	8
8-12	180	0.1	18	899	0	

Xu ∞ = 899 mg

- How to calculate ARE at :
  - ✓ **Time = 1 hr →** Xu∞ - Xu
    = 899 - 331.5 = 567.5 mg
  - ✓ **Time = 5 hr →** Xu∞ - Xu
    = 899- 813.5 = 85.5 mg

- **So we said that we plot ARE on the Y-axis, what about the X-axis (time) which time do we plot (remember the time is an interval)?**
  In the rate method, we used the middle point T-mid of the interval, but in the Sigma minus method, we used the end of the interval. **Why?** because in finding ARE we depend on the axis which is a cumulative value.



- Y-intercept: Xu∞ = 900.

- Note: There's no need for extrapolation because at time zero, we already know the amount of drug in the body (the amount yet to be excreted in the urine).

- The dose is 1000, while Xu∞ is 900, meaning 90% of the drug undergoes renal elimination.
- Since Xu∞ - Xu = 90%, this indicates that 90% of the drug is excreted unchanged through the renal system.

- **Sigma minus method:** in order to find an ARE we first added Xu values together to find Xu∞, this summation process as a sign of Sigma (δ)
  Then we subtract Xu from Xu∞ sign of subtraction (-) this is why it is **called the sigma minus method**.

Rate Method	Sigma minus Method
Rate of a drug appearance in urine Vs T-mid	Amount of drug remaining to be eliminated Vs T-end
(ΔXu /Δt) Vs T-mid	(Xu∞ - Xu) Vs T-end
Y-intercept = Kr Xo	Y-intercept = Xu∞
Fraction of a drug execrated unchanged by urinary system= (Kr / K)	Fraction of a drug execrated unchanged by urinary system= (Xu∞ / Xo)
Slope = -K	Slope = -K

- **Factors can make it difficult to obtain valid urinary excretion data:**
  - A significant fraction of the unchanged drug must be excreted in the urine.
  - The assay technique must be specific for the unchanged drug and must not include interference due to drug metabolites that have similar chemical structures.
    Remember: metabolism makes metabolites more water-soluble (more hydrophilic) so they can be eliminated by the renal system, so it's easy to be confused between soluble metabolites and unchanged drug in urine. We need a suitable method that can differentiate between unchanged drugs and metabolites in urine, for example, HPLC: "high-performance liquid chromatography" because. It separates the compounds before testing them. While using UV alone is not valid because. It can't differentiate between different bonds.
  - Frequent sampling is necessary for a good curve description.
  - Urine samples should be collected periodically until almost all of the drug is excreted.
    We need complete excretion to get Xu ♾. We said earlier that practically, the drug needs 5 half-lives to be totally eliminated, but here in urine, we need 7 half-lives to assume that we reached total elimination of the drug through urine.
  - Variations in urinary pH and volume may cause significant variations in urinary excretion rates.
    Changing the pH could change the reabsorption of the drug by inducing ionization (unionized drug molecules tend to be reabsorbed more than ionized ones) this is why we advise volunteers NOT to take any dietary that would affect urine pH (bicarbonate or lemon juice).
  - Subjects should be carefully instructed as to the necessity of giving a complete urine specimen we need to do a complete emptying of the bladder at the end of each interval.

- Regarding these factories, where would they have a higher effect? on Rate method or sigma Minus method? Let's compare the two methods:

➢ loss of urine sample

Rate method	Sigma-Minus method
It doesn't require knowledge of Xu ∞	Requires an accurate determination of Xu∞
loss of one urine specimen does not invalidate the entire urinary drug excretion study.	A small error in the assessment of Xu∞ introduces an error in terms of curvature of the plot, because each point is based on log (Xu∞ – Xu) versus time .
Both slope and intercept remain the same.	Both slope and intercept will change.

✓ **How to know if we have lost a sample of urine?**

Check If time intervals are continuous or not: each interval should start with the last time of the previous interval.

Time intervals	Volume	Conc
0-1	…	…
1-2	…	…
3-4	…	…

- Notice here we have a gap between second and third intervals second interval ends with (2) while the third interval starts with (3)! this indicates that we have lost amount of urine which means we are going to deal with rate method only.

➢ No complete emptying of the bladder

✓ The volume differs, for example, let's assume that after the third interval, there was no complete emptying of urine (we emptied 100 ml instead of 140 while the other 40 remained to the next time interval).

How would this affect both methods?

Time interval	Volu (ml)	Conc (mg/ml)	Amount	Xu	ARE	T-end
0-1	65	5.1	331.5	331.5	567.5	1
1-3	114	3.0	342	673.5	225.5	3
3-5	~~140~~ 100	1.0	140	813.5	85.5	5
5-8	225 +40	0.3	67.5	881	18	8
8-12	180	0.1	18	899	0	

Rate Method	Sigma Minus Method
A volume change will lead to a change in concentration on this change in the rate the third interval will have an increased rate while the fourth interval will have a decreased rate. This will lead to different plots (different slopes and intercepts).	Xu ∞ is the summary of all Xu values, so it will remain the same due to changes in Xu, this method will be affected but much less than the Rate method.

- **How to find Kr from:**
  - **Rate method?** From the Y-intercept
    Y-intercept = Kr Xo

  - **Sigma minus method?** We can't find it directly, instead, we use Xu ∞ and Xo to find it:
    (Xu∞ / Xo) = (Kr / K)

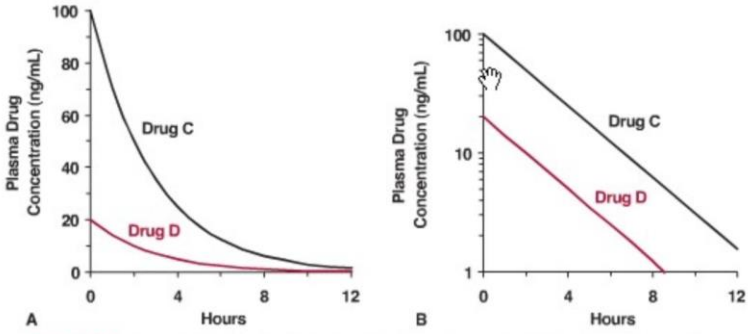


FIGURE 3-2. Drugs C (black line) and D (colored line) have the same half-life but have different initial concentrations and total exposure–time profiles. **A.** Regular (Cartesian) plot. **B.** Semilogarithmic plot. Doses of both drugs are the same.

  - **Do C and D have the same half-life?**
    Same half-life = same slope
    We can't know the slope here because it's in NORMAL paper.

  - **From the normal paper:**
    Drug C: A dose of 100 decreases to 50 after 2 hours.
    Drug D: A dose of 20 decreases to 10 after 2 hours.
    Both drugs have the same half-life because they take the same amount of time to decrease by one half-life.

THE END

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