Pharmacokinetics

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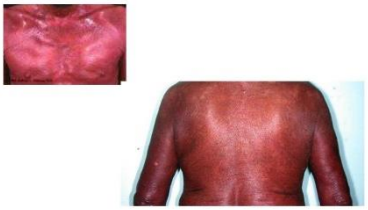
Pharm D. Heba Al-jammal

ARKAN ACADEMY

Intravenous Infusion

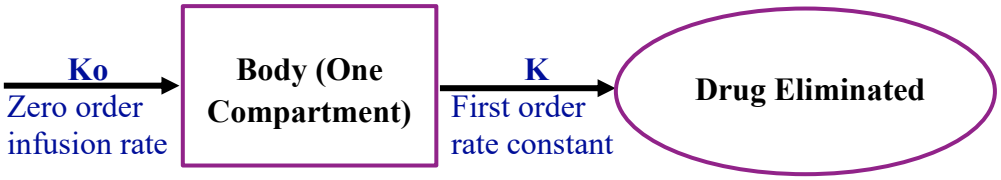
- It's about giving a constant amount in the blood through a certain time, so the **input** of the drug is **zero order rate** process because the input rate is constant.
- **Zero order infusion rate** is assigned as **Ko**, notice that this is the rate, because the rate is constant.
- Ko = rate of infusion = **(amount/time)**

- **Disadvantages of giving infusion drugs:**
  - The patient needs to be ***hospitalized*** but it's not a problem if the patient is already in the hospital.
  - Drugs given through infusion with other fluids should be checked for ***compatibility*** and ***stability***.
  - Some drugs cannot be given by rapid intravenous injection. Therefore, they may be given by short slow IV infusion over 15 or 30 minutes.
    - ✓ **Example**: Vancomycin: if given as a whole IV bolus, it would cause red man syndrome, to prevent this side effect Vancomycin is given as an IV infusion (500 mg over 30 min)



- **Why do we give IV infusion instead of IV bolus?**
  - To avoid fluctuations in plasma concentration: administering the drug intravenously in bolus doses leads to a rise in concentration to its peak followed by a gradual decline until reaching a minimum level. Subsequent doses repeat this pattern until a steady state is achieved.
    These ups and downs are fluctuations – تذبذبات

    We want to avoid these fluctuations:
    - ✓ To ensure a constant supply of the drug within the therapeutic range
    - ✓ To achieve consistent pharmacologic response (Constant concentration constant response)
    - ✓ To avoid certain side-effects
      Examples: vancomycin → red man syndrome.
      Aminoglycosides → severe hypotension and collapse if given as IV bolus.
  - To determine an accurate assessment of total body clearance: The best way to have an accurate clearance value is through IV infusion (will be discussed later)



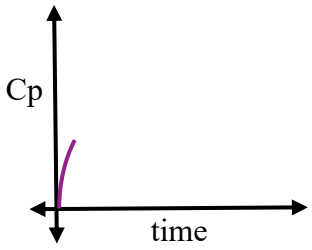
- So the rate of input is a zero order = Ko (amount/time)
- The rate of output is first order = KX
- If we want to calculate the change in drug amount in the body at certain time:

$\frac{dX}{dt}$ = Input-output

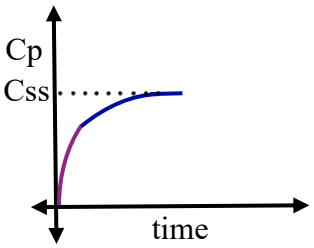
$\frac{dX}{dt}$ = Ko – KX

Why (–) ? Because it's a loss process The drug we input is lost by elimination

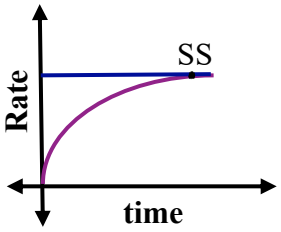
- At zero time :
  input rate = Ko (because It's constant)
  Output rate = zero (no drug to be eliminated yet)
  So, $\frac{dX}{dt} = Ko$



- After a time let's say 10 minutes
  Input rate = Ko (because It's constant)
  Output rate = KX (there is an elimination now)
  So, $\frac{dX}{dt} = Ko - KX$
  As we have an output rate, the plasma concentration is little decreased.



- As time Increases, the input rate will be constant, the output rate will increase and the slope will decrease. These changes continue until we reach a certain state where :-
  Input = output
  Ko = K *Xss , this is reached in a steady state (no changes)
  Xss: Is the amount of drug in steady state condition Xss / Vd = Css
  Css: is the concentration of a drug in steady-state condition Css is constant for a certain drug in certain patient (same clearance).



- So when do we reach a steady state?
  When input = output
  Ko = K Xss
  Xss = Ko/K
  Xss = Css*Vd

- Now for the equation, this is a growth function $(1 - e^{-kt})$
  $Cp = Css\ (1 - e^{-kt})$
  Plasma concentration will increase exponentially from a value of (zero to Css)
  - ✓ **At times zero:**
    Cp = Css * (1 – 1)
    Cp= zero
  - ✓ **At time ∞**
    Cp = Css*(1-0)
    Cp = Css

- So, Css = Xss / Vd
  Css = Ko / (KVd)
  Css = Ko /Cl

  Css = Ko/CL , this could be extremely useful in calculating clearances. When I have a table of drug concentrations at different time points, I can identify the steady-state by observing when the concentrations stabilize. At this point, I can calculate CL directly using the equation without needing to plot.

- Conclusion:
  - $X = Xss\ (1 - e^{-kt})$

    $X = \frac{Ko}{K}\ (1 - e^{-kt})$

  - $Cp = Css\ (1 - e^{-kt})$

    $Cp = \frac{Ko}{KVd}\ (1 - e^{-kt})$

    $Cp = \frac{Ko}{CL}\ (1 - e^{-kt})$

    $Css = \frac{Ko}{KVd}$
- IV infusion: there is a growth in conc. As time increases, after a certain period of time we will reach a steady state where we have concentration Css.

- Remember: Ko: Infusion rate

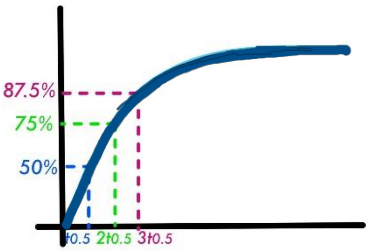
  K: elimination rate constant

- Concentration after 1 half-life

  $Cp_{t0.5} = Css\ (1 - e^{-k*t0.5})$

  $Cp_{t0.5} = Css\ (1 - 0.5)$

  $Cp_{t0.5} = 0.5\ Css$



After **1 t0.5** we reach **50%** of the steady-state concentration

After **2 t0.5** we reach **75%** of the steady-state concentration

After **3 t0.5** we reach **87.5%** of the steady-state concentration

(The growth is exponential)

- Let's go back to the equation:

$Cp = Css*(1- e^{-kt})$

$Cp = Css - Css*e^{-kt}$

$(Css - Cp) = Css*e^{-kt}$

$Log(Css - Cp) = logCss - \frac{K}{2.303}\ t$

$ln(Css - Cp) = lnCss - kt$

So when we plot them on normal paper:

Y- Axis = Log (Css – Cp) or Ln (Css – Cp)

X-axis = time

Slope = -k or $\frac{-K}{2.303}$

Y-intercept = Css

- Estimating PK-parameters
  - During Infusion
    - ✓ Half-life
    - ✓ Clearance
    - ✓ Volume of distribution
  - Post-Infusion

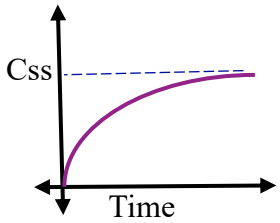
- **During infusion:**

Time	Cp
T1	C1
T2	C2
T3	C3
T4	C3

- We continue taking blood samples until the conc is constant.

(notice that we have the same conc. on t3 and t4) this means we have reached the steady state.

This is on normal paper.



If we want to draw it on semi log paper:

- ✓ On Y-axis we plot (Css – Cp), so we need to add a new column.

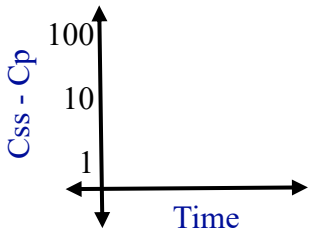
Time	Cp	Css - Cp
T1	C1	C3 – C1
T2	C2	C3 – C2
T3	C3	C3 – C3 = Zero
T4	C3	C3 – C3 = Zero

C3 = Css

Now we can plot:

- ✓ The first point is when Concentration in plasma is zero:

  Css – zero = Css
- ✓ As plasma concentration increases the difference between Css and Cp decreases.



- We are plotting how much remains of Cp until it reaches Css, which is a concept highlighted in the urinary elimination module, specifically through the sigma minus method.
- In sigma minus method: we draw amount remaining to be excreted.
  In IV infusion: we draw concentration remaining to reach steady state.

Back to our plot :

- ✓ Y-intercept = Css
- ✓ Slope = -K or (-K / 2.303)
- ✓ K is elimination rate constant and not infusion rate

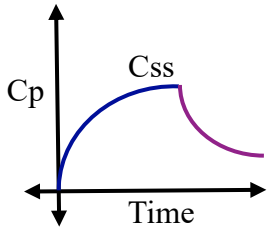
How to calculate PK parameters during infusion?

- ✓ Cl = Ko / Css
  Note that we do not need any plot to find CL
- ✓ Vd = Cl/ K
- ✓ $t_{0.5}$ = 0.693/ K

- All of this was during infusion, what about after infusion?

- **Post infusion:**
  - After stopping/Cessation / truncation of infusion no zero order input, just first order output (elimination). This means we are back on the same situation of IV bolus where only elimination process is taking place
  - The equation used in IV bolus => $C = Co\ e^{-kt}$
  - Stopping infusion can be either :
    - ✓ After reaching SS.
    - ✓ Before reaching SS.

- **After reaching SS:**



The initial conc for elimination is Css

Co = Css

$C_{post} = Css\ e^{-ktpost}$

- ✓ C_{post}: concentration after stopping infusion.
- ✓ t_{post}: time after stopping infusion (not during infusion).

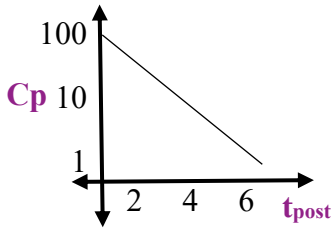
- Example: what is conc. 3 hrs after stopping infusion, knowing that SS is reached?

  $C_{post=3} = Css\ e^{-k*3}$

- Example:

Time (hr)	Cp (mg/L)
1	C1
2	C2
4	C3
6	C3
8	C4
10	C5
12	C6

- We stopped infusion after 6 hrs
  8: 2 hrs after stopping
  10: 4 hrs after stopping
  12: 6 hrs after stopping
  } We plot those conc-time



Y- intercept = Css

Slope = -K or (-K/

- **How to calculate PK parameters after stopping infusion (and reaching SS)**
  - ✓ Cl = Ko / Css
  - ✓ Vd = Cl/ K
  - ✓ t0.5 = 0.693/ K
- Until now we can find all the parameters during and after infusion, when we have reached SS.

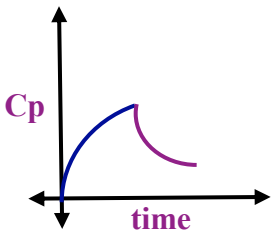
- **What happens if I stopped the infusion before reaching SS?**

- **Before reaching SS:**

Initial concentration is Co not Css

$C_{post} = Co\ e^{-k*t.post}$

Co: concentration when infusion is stopped (it is NOT Css)



How to calculate Co?

$Co = \left(\frac{Ko}{KVd}\right)(1-e^{-k*t.infusion})$ - The same equation we used before reaching Steady state.

$C_{post} = C\ initial * e^{-k*t.post}$

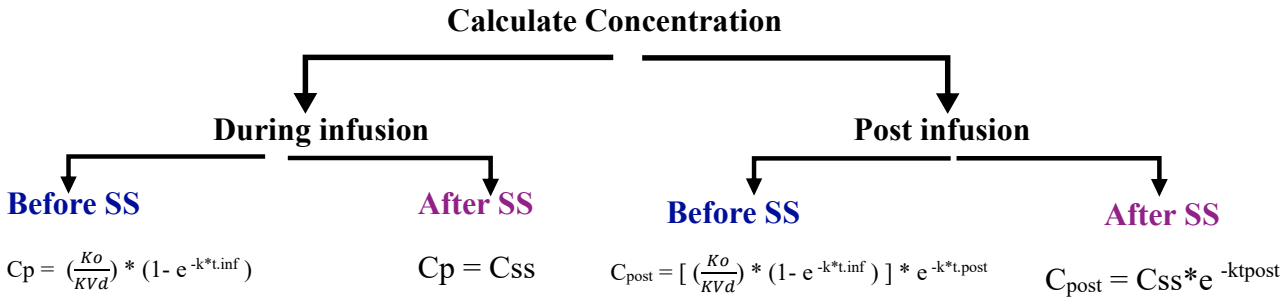
$C_{initial} = \left(\frac{Ko}{KVd}\right) * (1- e^{-k*t.infusion})$

$C_{post} = \left[\left(\frac{Ko}{KVd}\right) * (1- e^{-k*t.infusion}) \right] * e^{-k*t.post}$

$t_{infusion}$: time during infusion

t_{post}: time after stopping infusion

- **Conclusion:**



- **Example:** If a drug is infused intravenously at a rate of 50 mg/hr for 6 hours. The average pharmacokinetic parameters for this drug are:(K = 0.2 hr-1, Vd = 20 L)

  - **What is the conc. at 3 hrs after starting the infusion?**

    $Cp = (\frac{Ko}{KVd}) * (1- e^{-kt})$

    $Cp = (\frac{50}{0.2*20}) * (1- e^{-0.2*3})$

    Cp = 5.64 mg/L

  - **What is the conc. at 6 hrs after starting the infusion?**

    $Cp = (\frac{Ko}{KVd}) * (1- e^{-kt})$

    $Cp = (\frac{50}{0.2*20}) * (1- e^{-0.2*6})$

    Cp = 8.74 mg/L

  - **What is the conc. at 9 hrs after starting the infusion?**

    (6 hrs during infusion + 3 hrs post infusion)

    $C_{post} = [(\frac{Ko}{KVd}) * (1- e^{-k*t.inf})] * e^{-k*t.post}$

    $C_{post} = (\frac{50}{0.2*20}) * (1- e^{-0.2*6}) * e^{-0.2*3}$

    $C_{post} = 8.74 * e^{-0.2*3}$

    C_{post} = 4.8 mg/L

  - **What is the conc. at 3 hrs after stopping the infusion?**

    (6 hrs during infusion + 3 hrs post infusion)

    $C_{post} = [(\frac{Ko}{KVd}) * (1- e^{-k*t.inf})] * e^{-k*t.post}$

    $C_{post} = (\frac{50}{0.2*20}) * (1- e^{-0.2*6}) * e^{-0.2*3}$

    $C_{post} = 8.74 * e^{-0.2*3}$

    C_{post} = 4.8 mg/L

- **What is the conc. at 20 hrs after starting the infusion?**

  (6 hrs during infusion + 14 hrs post infusion)

  $C_{post} = [(\frac{Ko}{KVd}) * (1- e^{-k*t.inf})] * e^{-k*t.post}$

  $C_{post} = (\frac{50}{0.2*20})* (1- e^{-0.2*6}) *e^{-0.2*14}$

  $C_{post} = 8.74* e^{-0.2*14}$

  $C_{post} = 0.53$ mg/L

- **What is the conc. at 14 hrs after cessation of the infusion?**

  (6 hrs during infusion + 14 hrs post infusion)

  $C_{post} = [(\frac{Ko}{KVd}) * (1- e^{-k*t.inf})] * e^{-k*t.post}$

  $C_{post} = (\frac{50}{0.2*20})* (1- e^{-0.2*6}) *e^{-0.2*14}$

  $C_{post} = 8.74* e^{-0.2*14}$

  $C_{post} = 0.53$ mg/L

- **Css = Ko / Cl**

  Cl is constant, which means that the only factor that can affect steady state conc is infusion rate Ko (if we want to increase Css, we increase Ko. And vice- versa)

- To determine if we reached SS or not, by calculating time required to reach SS

  $Cp = Css (1- e^{-kt})$

  $\frac{Cp}{Css} = 1- e^{-kt}$ $(\frac{Cp}{Css})$ = fraction of steady state (Fss)

  $Fss = 1- e^{-kt}$

  $e^{-kt} = 1 - Fss$

  $t = \frac{\ln (1-Fss)}{-K}$ $k = 0.693/t0.5$

  $t = -1.44 * t0.5* \ln (1-Fss)$ Where t is time needed to reach any fraction of SS

  The time required to reach any fraction of SS depends only on the half life of the drug.

- **Remember**: at the beginning we said that:
  - After 1 t0.5 we reach 50% of steady-state concentration.
  - After 2 t0.5 we reach 75% of steady-state concentration.
  - After 3 t0.5 we reach 87.5% of steady-state concentration.

- Let's approve it …

What is the time needed to reach 50% of Css?

t = -1.44 * t0.5* ln (1-Fss)

= -1.44 * t0.5* ln (1-0.5)

= -1.44 * t0.5* 0.693

= t0.5 we reach 50% of Css after 1 half life

What is the time needed to reach 75% of Css?

t = -1.44 * t0.5* ln (1-Fss)

= -1.44 * t0.5* ln (1-0.75)

= 2 t0.5 we reach 75% of Css after 2 half-lives And so on …

$t_{90\%}$= 3.32 t0.5

$t_{95\%}$= 4.32 t0.5

$t_{99\%}$ = 6.64 t0.5

So, half life is the factor that determines time required to reach certain fraction of Css.

Time needed to achieve steady-state

Time (hr)	number of $t_{½}$ elapsed	fss
10	1	0.500
20	2	0.750
30	3	0.875
40	4	0.937
50	5	0.969
60	6	0.984
70	7	0.992
80	8	0.996
$t_{1/2}$	10 hr	
k_{el}	0.0693 hr^{-1}	

- When we note that 10 = $t_{0.5}$, we observe the following:
  After 1 $t_{0.5}$, we reach 50% of Css.
  After 2 $t_{0.5}$, we reach 75% of Css, and so on.
  After 5 $t_{0.5}$, we reach more than 95% of Css.

  This is why we assume that Css is reached after 5 $t_{0.5}$.

- **Practically**, steady state (SS) is attained after **5 half-lives**, whereas **theoretically**, it takes an **infinite (∞) time** to reach it.
- Notice that the same principle applies here as with **elimination in IV bolus**, but in this case, the concentration **increases** instead of decreasing (and at the same rate).
- The **infusion rate** is constant in this scenario, so it does not affect the process. The only factor influencing the outcome is the **elimination process**.

- **Question 1: At SS all drugs infused at the same rate and having same t0.5 reach the same:**
  A) Css
  B) Ass

  Answer: A) Ass

  Same half-life = same k
  Same rate = same Ko

  Will they have the same amount and the same concentration?

  From the equation:
  $Css = Ko / (K \times Vd)$
  $Xss = Ko / K$

  The equation for the amount depends only on k and Ko, and since they are the same for both drugs, the amount will also be the same.

  However, the equation for the concentration also depends on Vd, and since I don't have information about Vd, the answer will be B.

- **Question 2: What is/are the control factor(s) for tss?**

  Answer: tss depends only on half life.

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Arkan academy
Arkanacademy
www.arkan-academy.com
+962 790408805