Pharmacokinetics

2025-2024

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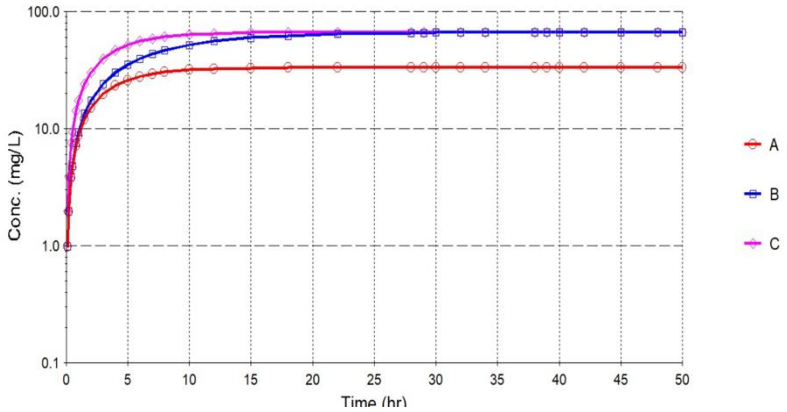
ARKAN ACADEMY

Relationship between K, Ko and Css



Case	Ko (mg/hr)	K (hr^{-1})	Vd (L)	Css (mg/L)
A	100	0.3	10	33.33
B	100	0.15	10	66.67
C	200	0.3	10	66.67

- **A:**

  Assuming A is the reference.

  Half life is 2.31 hr so the **time** needed to reach **SS** is 11.5 hr (point X)

- **B:**

  B had longer half life (lower k) so time needed to reach SS was longer (point Y)

  Half life is **doubled** to 4.62 hr, so **tss** is **doubled** to 23 hr.

- **C:**

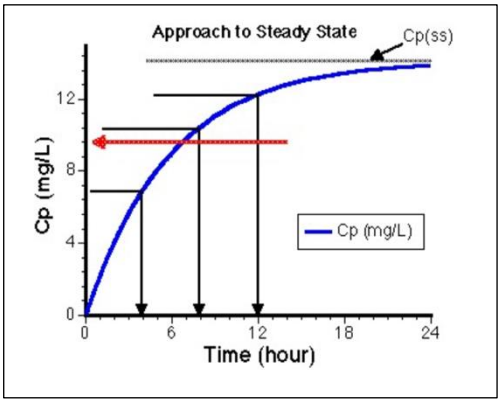
  We doubled rate of infusion in C, so we got higher Conc.

  The **Half life** is the **same** = 2.31**,** so the **time** needed to reach **SS** is the **same** = 11.5 hr(point X)

  - Remember as the Time required to reach SS is dependent on half-life, we need 5 half lives to reach/attain SS.
  - And if we have a drug that has **a long half-life** then the time required to reach SS will also be long, this is not practical! I can't wait 5 half-lives to reach SS!

    Let's take an example…

➢ **Example:**



➢ In this case we need around **20 hours** to reach SS, the patient will not stay this long period of time with no concentration of a drug in his body.

➢ So we need to increase the dose in the beginning by administrating **LOADING DOSE**, it is usually giving in form of IV bolus

- This IV bolus must be ideal, this means that it must give us an amount equal to the amount of SS (it must give Xss)

  Remember: Xss = (Ko / K) = (Css*Vd)

  So, the **initial concentration** would be **Css**

  Remember: Css = Xss / Vd

  Also remember in calculating concentration of IV bolus, we use this equation:

  $C = Co * e^{-kt}$

  And we said that initial concentration is Css, so the equation is: $\mathbf{C = Css * e^{-kt}}$ (this is IV bolus equation)

  So, we give IV bolus and start IV infusion at the same time

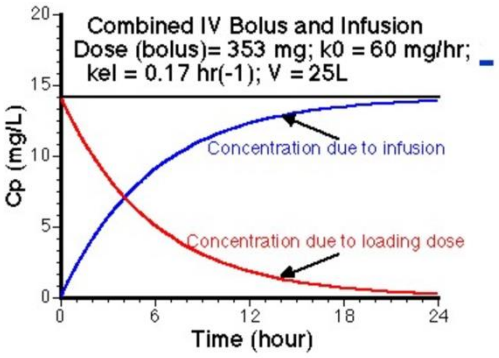
  The drug is given by both routes (the concentration is increasing from both routes)

  C_{total} = **IV bolus** + **IV infusion**

  $Ct = (Css*e^{-kt}) + (Css* (1 – e^{-kt})$

  $Ct = Css* e^{-kt} + Css – Css* e^{-kt})$

  Ct = Css: This means that when we give IV infusion and IV bolus (loading dose) the concentration at any time would be equal to CSS.



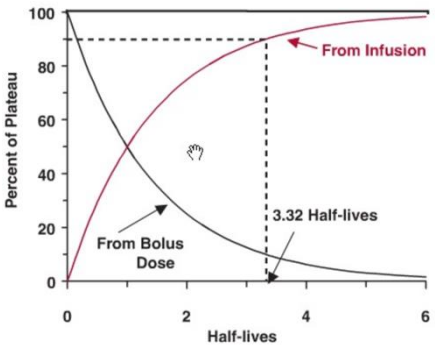
- Let's approve what we said and term of half life:

- **For IV infusion** (exponential increase)

  After 1 half-life: Increasing into 50% of SS

  After 2 half-lives: Increasing into 75% of SS

  After 3 half-lives: Increasing into 90% of SS



- **For IV bolus** (exponential decrease)

  After 1 half-lives: 50% loss of SS (remaining is 50%)

  After 2 half-lives: 75% loss of SS (remaining is 25%)

  After 3 half-lives: 90% loss of SS (remaining is 10%)

- So: after 1 half-life: (50% infusion + 50% bolus = **100% SS**)

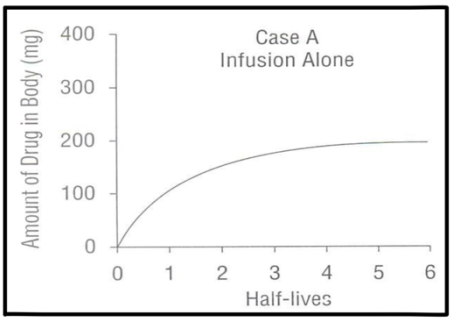
  After 2 half-lives: (75% infusion + 25 % bolus = **100% SS**)

  After 3 half-lives: (90% infusion + 10 % bolus = **100% SS**)

  The total concentration will always be equal to Css

- **So, loading dose lead to attaining Css immediately (from time zero)**

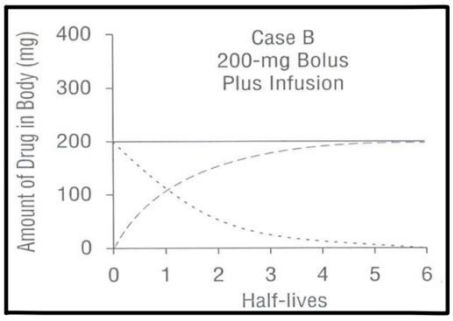
- **What if loading dose was not ideal (doesn't give Xss)? let's study the following to answer this question…**



Case A :

We found that Xss = 200 mg through testing IV infusion.

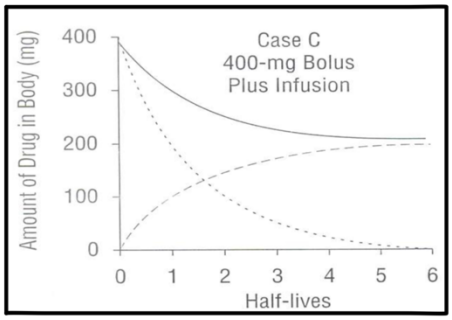
Here, no loading dose was given—only an infusion was started to determine the **Xss**.



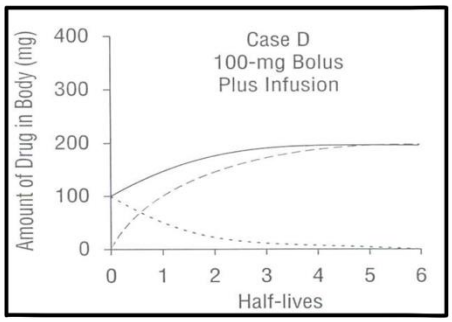
Case B: If we give IV bolus of 200 mg (equals to Xss), this is an ideal loading dose, we will reach SS from time zero!

after 1 half life the IV bolus dose will decrease to 100, while IV infusion will increase to 100, so the total is 200 and so on…

They will continue to complement each other to maintain the amount at **200 mg** and stay at steady state (SS).



Case C: If we give IV bolus dose of 400 mg (higher than Xss) , after 1 half-life IV bolus will decrease to 200 while IV infusion will increase to 100, total is 300 after 2 half lives, IV bolus as well decrease into 100 while IV infusion will increase into 150, total is 250
When will we reach total of 200 (Xss) ? practically after 5 half-lives , this means that we didn't reach SS immediately but after 5-7 half lives.



Case D: If we give loading dose of 100 (less than Xss) after 1 half life IV bolus will decrease into 50 while IV infusion will increase up to 100 , the total is 150 and so on …
we will reach SS after 5 to 7 have lives (not immediately)

This means that if loading dose not equal Xss we will NOT reach SS immediately, we will reach it after 5 half lives.

- So, this way I didn't gain anything, because even without giving a loading dose, I would still have to wait **5 half-lives** to reach steady state (SS). And if I gave the loading dose incorrectly, I would still end up waiting the same time.
- So in situations A, C, D we will wait 5 half-lives to reach SS, we reach SS immediately only if loading dose = XSS

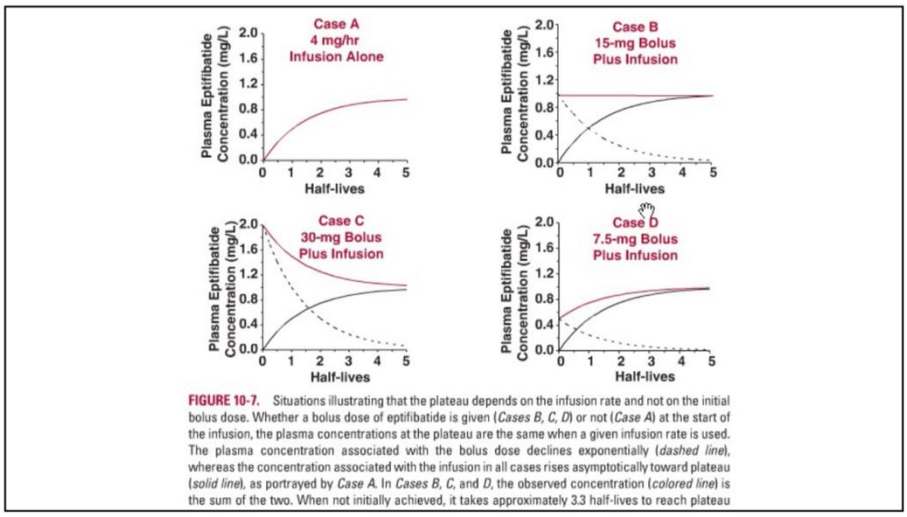


FIGURE 10-7. Situations illustrating that the plateau depends on the infusion rate and not on the initial bolus dose. Whether a bolus dose of eptifibatide is given (*Cases B, C, D*) or not (*Case A*) at the start of the infusion, the plasma concentrations at the plateau are the same when a given infusion rate is used. The plasma concentration associated with the bolus dose declines exponentially (*dashed line*), whereas the concentration associated with the infusion in all cases rises asymptotically toward plateau (*solid line*), as portrayed by *Case A*. In *Cases B, C,* and *D*, the observed concentration (*colored line*) is the sum of the two. When not initially achieved, it takes approximately 3.3 half-lives to reach plateau

- It is almost impossible to know Xss before attempting an IV infusion and testing it in the patient. This brings us to the next question:

- **Is it helpful to use a loading dose?**

In most cases, we don't even know the exact amount to give, and we might mistakenly administer a dose that is either less or higher than **Xss**, which would make it take longer to reach steady state (SS).

- **Do you still think it is helpful to give a loading dose?**

Actually, **yes, it is helpful** because giving an incorrect amount in the loading dose (either higher or lower than **Xss**) will only slow down the time to reach a constant concentration (Css). However, it will **speed up the onset of action**, helping the drug enter the therapeutic window faster and achieve an effect sooner.

- **Key point:**
  - Increasing or decreasing the loading dose allows for **faster therapeutic effects**, even though it slows the time required to stabilize the concentration.
  - The goal is not to immediately stabilize the concentration but to treat the patient and achieve the desired effect as quickly as possible.
  - We care more about having an **effect** than reaching **SS**. While we will attain **Css** after **5 half-lives**, we can achieve an effect in less than **1 half-life**!
  - Thus, adding a loading dose **reduces the onset of action** but may increase the time required to reach Steady state.
  - **The only concern** with a loading dose is if it results in a **toxic concentration**.

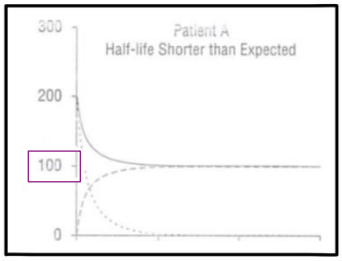
- **What if half life of our drug is changed ?**

  - First, how would the have life change for a drug ?
    Suppose our drug has Xss = 200 mg
    if we give another drug , and this drug was as **enzyme inducer** for metabolism of our drug (make it faster to eliminate our drug) so half life of our drug is shorter than expected and hence K is higher than expected.

  - Xss is decreased to 100 mg
    Css is decreased
    } Due to increased K : $(Css = \frac{Ko}{KVd})$ & $(Xss = \frac{Ko}{K})$

    And time required to reach SS (5 half-lives) well decrease because half life is decreased

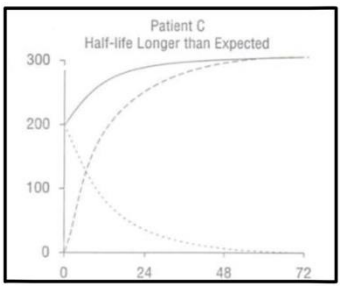
  - **So decreasing t0.5 will decrease :**
    - ✓ Css
    - ✓ Xss
    - ✓ Time required to reach SS



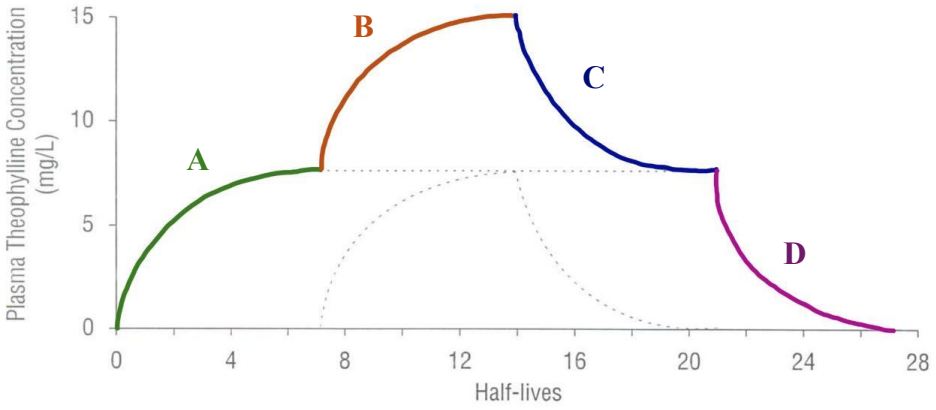
  - On the other hand if the second given medication is **enzyme inhibitor** for the metabolism of our drug (decrease elimination/ makes it slower to eliminate our drug) so half life of our drug will be longer and hence K is lower.

    - ✓ Xss is increased to 300 mg
    - ✓ Css is increased
    - ✓ Time to reach SS is increased

    So increasing t0.5 will increase Xss, Css and time required to reach SS.



- **Example : therapeutic range for this drug is 10 to 20 mg/L**



  - A) after giving this drug in an infusion rate Ko of 30 mg/h we reached SS after 5 to 7 half-lives and calculated Css = 7.5 mg/L (out of therapeutic range, no effect)
  - B) So we decided to increase Ko up to 60 mg/h to have higher CSS remember when clearance is constant (same patient) CSS increase by increasing Ko New Css = 15 mg/ L The change in Ko will break the equilibrium (point X) After increasing Ko the concentration will change until we attain new SS after 5 t0.5
  - C) Add a new Ko, new high Css, we might face some problems with the patient (side effects) so we need to decrease the rate again to the previous Ko This decrease will continue until we reach another SS (same SS when we give rate of A) after 5-7 half-lives
  - D) we want to stop the medication, so we stop the infusion (it is now like IV bolus; conc of the drug will decline and finally we will get rid of medication after 5 to 7 t0.5).

  - **Conclusion: changing infusion rate Ko requires 5 to 7 t0.5 to attain a new steady-state situation.**

- **Question 1:** How can I increase the concentration from **7.5 mg/L** to **15 mg/L** immediately without waiting for the initial SS through infusion?

  To achieve this, I would give an **IV bolus loading dose**.

  The required **amount** can be calculated as:
  Amount = (Target concentration - Current concentration) * Vd
  Amount = (15 - 7.5) * Vd = **7.5 * Vd**

- **Question 2:** How can I quickly increase the concentration from **4 mg/L** to **10 mg/L**?
  Similarly, I would give an **IV bolus loading dose**, and the required **amount** would be:
  Amount = (Target concentration - Current concentration) * Vd
  Amount= (10 - 4) * Vd = **6 * Vd**

- **Figure:**

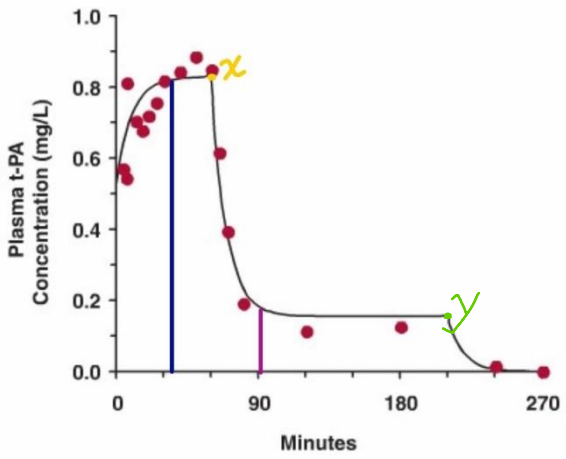


FIGURE 10-6. The plasma concentration of plasminogen activator (t-PA) starts at about 0.6 mg/L and approaches a plateau of 0.8 mg/L following an i.v. bolus of 10 mg and a constant-rate infusion of 1.6 mg/min for 60 min to an individual subject. Subsequently, the plasma concentration drops as the drug infusion is decreased to 0.3 mg/min until 210 min when the infusion is discontinued. The time from the first steady state to the second one (0.16 mg/L) depends on the half-life of the drug 6.6 min in this subject, as does the decline to zero after drug administration is stopped.

- A drug (**plasminogen activator**) has t0.5 = 6.6 minutes, if given in IV infusions, SS is reached after five t0.5: 5 * 6.6 = 33 min = almost half an hour (pointed in **blue**).
  At X: we changed Ko and reached a new SS after another 5 half-lives (another half hour) at 90 minutes (pointed in **purple**)
- **Did we increase or decrease Ko?** decrease it, because the plot declines.
  At Y: we stopped the infusion after another 5 half-lives (another half-hour) the concentration of the drug is almost 0.

- **If we want to know the time needed to reach SS we need to know the half life and then multiply it with five**.

- For Digoxin (t0.5 =34 hours) if it is infused for 72 hours would we reach SS or not?
  34 hr * 5 = 170 hr No, because 70 hours involves only 2 half-lives

  Although 70 hours is a long time, it is not enough to reach steady state (SS) for digoxin. However, 30 minutes was sufficient for a plasminogen activator and covered the 5 half-lives required.
  This shows that there is no absolute "long" or "short" time it is always relative to the drug's half-life.

  This model is applicable for any route of administration that involves zero order absorption.
  Oral: some dosage forms release drugs in zero order
  Transdermal
  Long acting IM injections
  Subcutaneous implants (contraceptives)
  Vaginal rings

  And here are many other examples…

Table 6–1. Representative Constant-Rate Devices and Their Applications

TYPE OF THERAPEUTIC SYSTEM	DRUG	RATE SPECIFICATION	APPLICATION/COMMENTS
Intravenous	Many drugs	Rate controlled by device	Used for i.v. infusion Some devices are portable, others are implantable
Oral	Nifedipine	30, 60, or 90 mg/day administered daily	Calcium channel blocker Nondisintegrating system is designed to provide a constant rate of release for 24 hr
	Phenylpropanolamine	25 mg immediate release and 3.4 mg/hr for 16 hr	Appetite suppressant System aims to provide a constant and effective plasma concentration of phenylpropanolamine for 16 hr
Transdermal	17β-Estradiol	0.05 or 0.1 mg/day	Treatment of menopausal symptoms and prevention of osteoporosis Applied to trunk of body, including buttocks and abdomen, twice weekly
	Nicotine	7, 14, and 21 mg/day (40 μg/cm²/hr) changed daily	Aid to stop smoking Provides a reasonably constant plasma concentration of nicotine Patch placed on front or back above waist or on upper outer part of arm
	Nitroglycerin	2.5, 10, and 15 mg over 24 hr	Prophylaxis against attack of angina pectoris System aims to provide a constant plasma concentration of nitroglycerin Recommended application site is lateral chest wall
	Scopolamine	0.5 mg over 3 days	Used for prevention of motion sickness Applied to hairless area behind ear at least 4 hr before the antiemetic effect is desired

TABLE 10-2 Representative Constant-Rate Devices or Systems and Their Applications

Type of Therapeutic System	Drug	Rate Specifications	Application/Comment
Intramuscular (i.m.) Injection	Haloperidol	Deep i.m. injection (50 and 100 mg/mL in sesame oil). Initial dose of 10–15 times dose of oral immediate-release product. Maintenance with once-monthly injection. Approximately 1/30th of the dose becomes systemically available daily, on average.	Used in treating schizophrenia patients who require prolonged parenteral therapy.
	Leuprolide	Dose depends on age of child (7.5, 11.25, and 15 mg per syringe). Starting dose is 0.3 mg/kg every 4 weeks.	Used in the treatment of children with central precocious puberty.
Oral	Glipizide	2.5, 5, or 10 mg release tablets administered once daily.	Oral blood glucose lowering drug of sulfonylurea class with 24 hr constant-rate release.
	Nifedipine	30, 60, or 90 mg/day administered once daily.	Nondisintegrating system is designed to provide a constant rate of release for 24 hr. Used in treating vasospastic and chronic stable angina and hypertension.
Subcutaneous Implant	Goserelin	Implanted subcutaneously Continuous release of drug for a 12-week period. Product is biodegradable.	Used in treating prostate carcinoma. Potent synthetic decapeptide analogue of luteinizing hormone-releasing hormone.
	Leuprolide acetate	Implant is nonbiodegradable Implanted subcutaneously and removed and replaced once yearly. Contains 72 mg of leuprolide acetate. Delivers 120 μg/day.	Used as palliative treatment of advanced prostatic cancer.

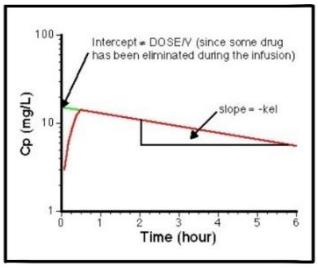
TABLE 10-2 Representative Constant-Rate Devices or Systems and Their Applications (*continued*)

Subcutaneous Injection	Insulin glargine	Exhibits a relatively constant glucose-lowering effect over 24 hr, permitting once-a-day administration.	Treatment of adult and pediatric patients with type I diabetes mellitus or adults with type 2 diabetes mellitus who require long-acting insulin for control of hyperglycemia.
Vaginal Ring	Etonogestrel/ ethinyl estradiol	On average, 0.12 mg of the progestin hormone and 0.05 mg of the estrogen are released per day.	Used to prevent pregnancy. Ring is inserted for 3 weeks. After a 1-week break, another is inserted.

TABLE 10-3 Examples of Transdermal Delivery Systems

Drug	Use	Delivery
Clonidine	Treatment of hypertension	Delivery of 0.1, 0.2, or 0.3 mg clonidine per day for 1 week.
Estradiol	Estrogen replacement, menopause	Constant rate of delivery. Applied twice to once weekly. Dosage is individualized.
Fentanyl	Continuous pain relief	Applied every 3 days.
Norelgestromin/ethinyl estradiol	Prevention of pregnancy	Weekly change of patch for 3 weeks. 1 week no patch.
Oxybutynin	Treatment of overactive bladder	Applied every 3–4 days.
Progesterone	Progesterone supplementation, secondary amenorrhea	Vaginally, twice daily for progesterone supplement, every other day for treating amenorrhea.
Scopolamine	Motion sickness	Effect lasts for 3 days (1.0 mg delivered).
Testosterone Patch, Gel Buccal system	Testosterone replacement therapy, male hypogonadism	Once-daily application.

- **Important note:** In IV infusion we can't find Co from extrapolation of the line We don't even have Co here (this is a common mistake in calculating Vd try to avoid it)

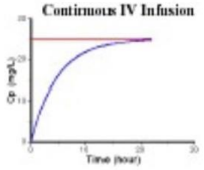


About "steady-state"

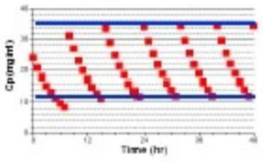
"steady-state" indicates at any time point, "rate in" = "rate out".

In practice, "steady state" is achieved when plasma concentration for this drug (peak, average, and trough) are identical at all time points following each administered dose given a fixed dose and dosing regimen, or in other words, the "rate/amount in" = "rate/amount out" for any period of time that is equal to dosing interval.

Continuous IV Infusion



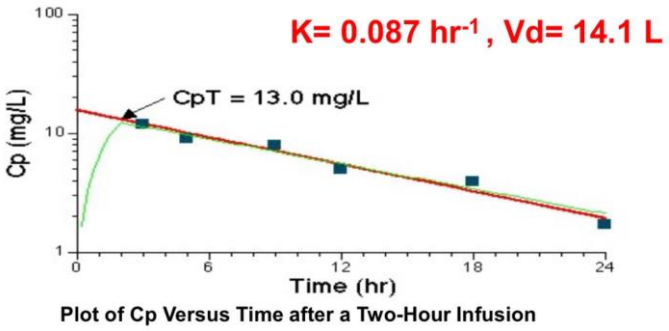
Multiple IV Bolus



Cases in IV Infusion

- **Case 1:** Following a two-hour infusion of 100 mg/hr plasma was collected and analyzed for drug concentration. Calculate K and Vd.

Time (hr)	3	5	9	12	18	24
Cp (mg/L)	12	9	8	5	3.9	1.7



Plot of Cp Versus Time after a Two-Hour Infusion

These conc in the table are collected in post infusion phase (after infusion) because the first conc is on 3 hr while the whole infusion took 2 hours only.

Ko = 100 mg/ hr
Xo = 100*2 = 200 mg

- **K ?**
  From slope we can find K
  -Slope = **K = 0.087 hr^{-1}**
  t0.5 = 8 hr, we didn't reach SS.

- **Vd ?**
  $Cp = [(\frac{Ko}{K*Vd})*(1 - e^{-k*tinfustion})]*e^{-k*tpost}$
  $12 = [(\frac{100}{0.087*Vd})*(1 - e^{-0.087*2})]* e^{-0.087*1}$
  Vd = 14.1 L

- **Case 2:** Estimate the volume of distribution, elimination rate constant, half-life, and clearance from the data in the following table obtained on infusing a drug at the rate of 50 mg/hr for 16 hours.

Time (hr)	0	2	4	6	10	12	15	16	18	20	24
Conc (mg/L)	0	3.48	5.47	6.6	7.6	7.8	8	8	4.6	2.62	0.85

Ko = 50 mg/L
Infusion time = 16 hr

Did we reach SS? yes, because the concentration is constant at both 15 and 16 hours
after 16 hours the infusion stopped.
Css =8 mg /L

- **Cl** = $\frac{Ko}{Css}$

  $= \frac{50}{8}$ = 6.25 L/hr

- **K ?** We can find K from the slope of post-infusion information (at times 18,20,24 hr)

  Slope = $\frac{\ln(4.6)-\ln(2.62)}{18-20}$ = -0.28 hr -1

  K = - Slope = 0.28 hr^{-1}

- **t0.5** = $0.693/K$ = 2.5 hr

- **Vd** = $\frac{Cl}{K}$

  $= \frac{\mathbf{6.25}}{\mathbf{0.28}}$ = 22 L

.....

- **Case 3:** A drug that displays one compartment characterstics was administered as an IV bolus of 250 mg **followed** immediately by a constant infusion of 10 mg/hr for the duration of a study. Estimate the values of the volume of distribution, elimination rate constant, half-life, and clearance from the data in the following table:

Time (hr)	0	5	20	45	50
Conc (mg/L)	10	7.6	4.8	4.0	4.0

Here we have IV infusion + IV bolus

Very important note:
At **times zero** the concentration is only from IV bolus.
At steady-state (**time 45, 50 hr**) the concentration is only from IV infusion.
In between (**time 5, 20 hr**) combination IV infusion + IV bolus.

- At times zero we have no infusion, so the concentration 10 mg/L is only from IV bolus
  IV bolus dose = 250 mg

  Vd = $\frac{Xo}{Co}$

  $= \frac{250}{10}$ = 25 L

- If you noticed a time 45 hr the concentration is constant this means that we reach it SS where the concentration is Css , Css is from IV infusion only
- **Cl** = $\frac{Ko}{Css}$

  $= \frac{10}{4}$ = 2.5 L/ hr
- Vd = Cl / K

  K = 0.1 hr^{-1}
- **Half-life** = 0.693 /0.1 = 7 hrs
- **Do not take any slope in combined IV bolus + infusion! you will get the wrong information.**

- **Case 4:** For prolonged surgical procedures, succinylcholine is given by IV infusion for sustained muscle relaxation. A typical initial dose is 20 mg followed by a continuous infusion of 4 mg/min. The infusion must be individualized because of variations in the kinetics of the metabolism of succinylcholine. Estimate the elimination of half-lives of succinylcholine in patients requiring 0.4 mg/min and 4 mg/min, respectively, to maintain 20 mg in the body.

  This drug has high variability between different patients, so we need to individualize the dose for each patient so that XSS remains 20 in the two patients.

  - Patient 1: we give an infusion of rate 0.4 mg/min
    Patient 2: we give an infusion of rate 4 mg/min

  - **What is the half-life for each patient?**
    1st patient:
    Xss = $\frac{Ko}{K}$
    20 = $\frac{0.4}{K}$ → **K=0.02 hr^{-1}**
    t0.5 = 0.693 / K
    t0.5 = 35 min

    2nd patient:
    Xss = $\frac{Ko}{K}$
    20 = $\frac{0.4}{K}$ → **K=0.2 hr^{-1}**
    t0.5 = 0.693 / K
    t0.5 = 3.5 min

- **Case 5:** A drug is administered as a short term infusion. The average pharmacokinetic parameters for this drug are: K = 0.40 hr^{-1} Vd = 28 L
  This drug follows a one-compartment body model.

  - **A 300 mg dose of this drug is given as a short-term infusion over 30 minutes. What is the infusion rate? What will be the plasma concentration at the end of the infusion?**
    Ko = Xo/ t.infusion = 300/ 30 = 10 mg/min
    If you were asked to find Ko in mg/hr => 300/0.5 hr = 600 mg/ hr
    At the end of infusion (at time 30 min) = we didn't reach SS! Because **half-life is 2.4 hr**.

    Cp = Css*(1 - $e^{-k*tinfusion}$)
    Cp = $(\frac{600}{0.4*28})$*(1 – $e^{-0.4*0.5}$)
    Cp = 9.71 mg/L

  - **How long will it take for the plasma concentration to fall to 5.0 mg/L?**
    t post infusion?
    Cp = C initial * $e^{-k*tpost}$
    5 =[$(\frac{600}{0.4*28})$*(1 – $e^{-0.4*0.5}$)]*$e^{-0.4*tpost}$
    5 = 9.71 * $e^{-0.4*tpost}$
    tpost = 1.66 hr

- **If another infusion is started 5.5 hours after the first infusion was stopped, what will the plasma concentration be just before the second infusion?**

  Cp?

  $Cp = Cintial * e^{-k*tpost}$

  $Cp = 9.71*e^{-0.4*5.5}$

  Cp = 1.08 mg/L

………

- **Case 6:** A patient is administered 60 mg/h of theophylline. It is known from previous hospital admissions that the patient has the following pharmacokinetic parameters for theophylline: V = 40 L and $K = 0.139\ h^{-1}$.

  - **What is the serum concentration of theophylline in this patient after receiving the drug for:**

    A) 8 hours

    Cp = Css*(1 - e^-kt)

    $Cp = (\frac{60}{0.139*40})*(1 - e^{-0.139*8})$

    Cp = 7.24 mg/L

    B) At steady state.

    $Css = \frac{60}{0.139*40}$

    Css = 10.8 mg/L

  - **Compute the theophylline serum concentration 6 hours after the infusion stopped in either circumstance (a & b)**

    A) **8 hours**

    $Cp = Cpt8 * e^{-ktpost}$

    $Cp = 7.24*e^{-0.139*6}$

    Cp = 3.14 mg/L

    B) **At steady state.**

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

    $Cp = 10.8*e^{-0.139*6}$

    Cp = 4.69 mg/L

………

- **Case 7:** A 20 year-old male patient with ideal body weight of 60- kg is receiving 950 mg of a cephalosporine infused intravenously over 15 minutes. The half-life of the drug is 45 minutes and the apparent volume of distribution is 0.8 L/kg. Find out :

  K= 0.693/0.75

  $= 0.924\ hr^{-1}$

  Vd = 0.8*60 = 48L

  - **The rate of infusion (mg/hr).**

    $Ko = Xo/ t.infusion$

    = 950/15

    = 63.3 mg/min → 3800 mg/hr

- **The onset of action (in min) if the MEC is 10 µg/ml.**

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

  $10 = (\frac{3800}{0.924*48})*(1 - e^{-0.924*t})$

  t = 0.14 hr*60 → 8 min

- **The maximum concentration after this infusion.**

  it's not Css! The higher conc. Is when the infusion has stopped (15 min/0.25h)

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

  $Cp = (\frac{3800}{0.924*48})*(1 - e^{-0.924*0.25})$

  Cp = 17.7 mg/L

……..

- **Case 8:** Shargel, 2016, Chapter 6, Q5. According to the manufacturer, a steady-state serum concentration of 17 mg/L was measured when the antibiotic, cephradine (Velosef ^{R}) was given by IV infusion to 9 adult male volunteers (average weight, 71.7 kg) at a rate of 5.3 mg/kg/h for 4 hours.

  Css = 17 mg/L

  Ko = 5.3*71.7 = 376.8 mg/h

  T infusion = 4 hr

  - **Calculate the total body clearance for this drug**.

    $CL = \frac{Ko}{Css}$

    = 376.8/17 = 22.4 L/hr

  - **When the IV infusion was discontinued, the cephradine serum concentration decreased exponentially, declining to 1.5 mg/L at 6.5 hours after the start of the infusion. Calculate the elimination half-life.**

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

    $1.5 = 17*e^{-2.5k}$

    K= **0.971 hr^{-1}**

    t0.5 = 0.693/0.971

    t0.5 = 0.714 hr

  - **From the information above, calculate the apparent volume of distribution.**

    $Css = \frac{Ko}{KVd}$

    $17 = \frac{376.8}{0.971*Vd}$

    Vd = 23 L

THE END

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