Pharmacokinetics

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ARKAN ACADEMY

One-Compartment Open Model: Intravenous Bolus Administration

- ***The one-compartment open model:***
  - Offers the simplest way to describe the process of drug distribution and elimination in the body.
  - This model assumes that:
    - ✓ The drug can leave the body (i.e., the model is "open").
      - Open model = Able to be eliminated.
    - ✓ The body acts like a single, uniform compartment (kinetic).
  - The simplest kinetic model that describes drug disposition in the body is to consider that:
    - ✓ The drug is injected all at once (Bolus) into a box (One compartment).
    - ✓ The drug distributes instantaneously and homogenously (kinetically) throughout the compartment.
    - ✓ Drug elimination also occurs from the compartment immediately after injection.
  - The simplest route of drug administration from a modeling perspective is a rapid intravenous injection **(IV bolus).**

One-compartment administration can be given in 3 way

No input over time	Zero order input	First order input
(IV Bolus)	(IV infusion)	(Oral)

- ***One-Compartment Open Linear Model Assumptions:***
  - **Rapid Mixing:** The drug is mixed instantaneously in blood or plasma.
  - **One compartment:** The drug in the blood/plasma is in rapid equilibrium with the drug in the extravascular tissues (no apparent distribution phase).
  - **Linear Model:** drug elimination follows first-order kinetics.
    - ✓ Elimination rate or change in concentration is proportional to the amount available for elimination.

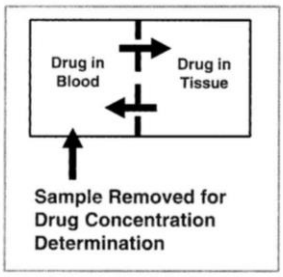


Figure 1.1. Blood is the fluid most often sampled for drug concentration determination.

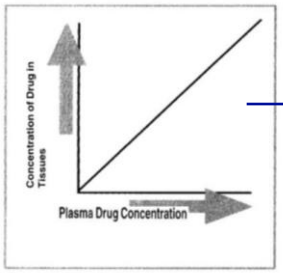


Figure 1.2. Relationship of plasma to tissue drug concentrations.

The Conc of drug in tissues is proportional to plasma drug conc because of equilibrium.

- **Figure 1.1 explains:**
  - Once a drug enters the blood, it is distributed to other organs and quickly reaches equilibrium.
  - The blood reflects or represents what's happening in the organs (kinetic homogeneity).
  - Remember, it **reflects but doesn't equal**! if the plasma concentration of a drug is decreasing, the concentration in tissues will also decrease, but not by the same amount or concentration. This property helps when adjusting doses for patients.

- **Figure 1.3** is a simplified plot of the drug concentration versus time profile following an intravenous dose, illustrating the property of kinetic homogeneity.
- This concept shows how the **blood reflects** what happens in the rest of the organs:
  - If the drug concentration is high in the plasma, it's high in the rest of the body.
  - If it decreases in the plasma, it decreases in the rest of the body as well.

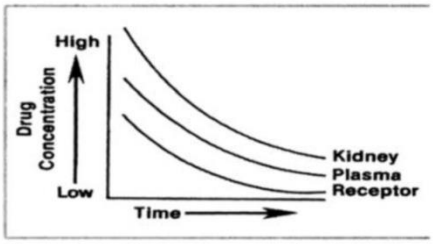
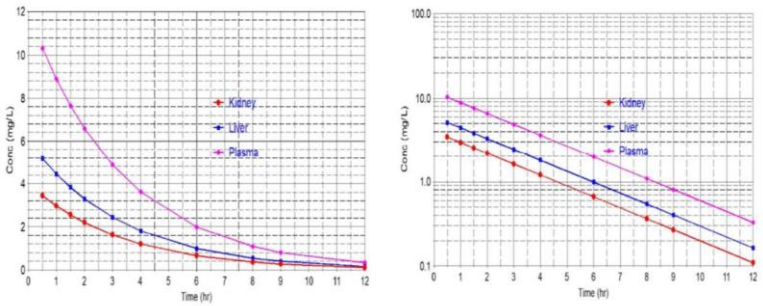


Figure 1.3. Drug concentration versus time.

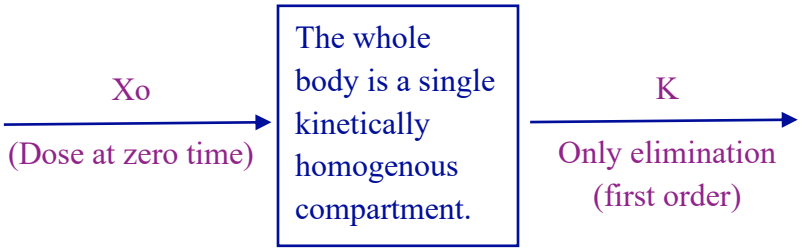
- The property of kinetic homogeneity is important for the assumptions made in clinical pharmacokinetics:
  - It is the foundation on which all therapeutic and toxic plasma drug concentrations are established.
  - That is, when studying concentrations of a drug in plasma, we assume that these plasma concentrations directly relate to concentrations in tissues, where the disease process is to be modified by the drug (e.g., the central nervous system in Parkinson's disease or bone in osteomyelitis). This is assumption, however, may not be true for all drugs.

- **Linear kinetics (First order)**

Normal paper Semi-log paper



- **IV Bolus:** It is the simplest way to describe the disposition (elimination).
  - Note: **Disposition** is all the process after Absorption (distribution & elimination)
  - But in the case of **IV bolus,** there is no distribution so the disposition is only elimination.



  - So the drug is injected all at once, as we give the dose /amount (Xo), all of it will be in the blood, simply:
    - ✓ At zero time: the amount is (**Xo**).
    - ✓ As the drug enters the blood, immediately the elimination process starts and the amount begins to decline (**Xt**).

- ***Are compartments specific parts of the body?***
  - **No**, they are ***hypothetical*** and not related to the ***anatomy*** or ***physiology*** of the body.
  - We divide them based on the ***organ's homogeneity***, with a one-compartment model indicating equilibrium across organs at the same time.

  - In **first-order kinetics**, the process is typically **linear**, but in the case of an IV bolus, there is no separate distribution phase. So, when we refer to first-order kinetics in this context, we are specifically discussing the **elimination process**, which is the only process that happens after the bolus is administered.
  - When we say the elimination process follows first-order kinetics, it means that the rate of elimination or the change in concentration is directly **proportional** to the amount of drug available for elimination at any given time.

    - ✓ Glomerular Filtration → Passive

    - ✓ Tubular secretion
      ✓ Biliary secretion
      ✓ Biotransformation
      } Involve **enzymatic processes** (active)

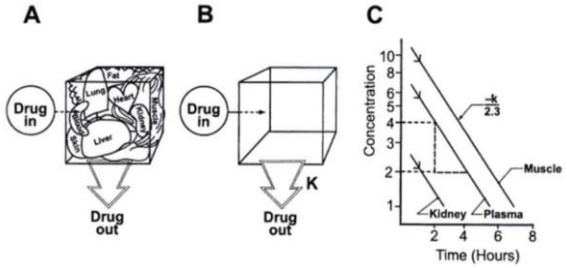
      - **Enzyme saturation** leads to zero-order kinetics, but IV bolus administration usually follows first-order kinetics, how does this work?
        This is because most therapeutic drug concentrations are too low to saturate enzymes, so elimination remains proportional to concentration. Only at very high levels does saturation occur.

- **Question:** With a drug that follows **first-order elimination**, the amount of drug eliminated per unit time:

  A) Remains constant while the fraction of drug eliminated decreases.
  B) Decreases while the fraction of drug eliminated remains constant.

  Answer: B) Decreases while the fraction of drug eliminated remains constant.

One-Compartment Model: IV Bolus Dosing



- **Xt:** the <u>amount</u> of drug remained in the compartment
- **K:** first-order elimination rate <u>constant</u> (OVERALL) (unit = time^{-1})

Rate of elimination = dX/dt = -KX

- **Notice:** K is the rate constant not the rate itself, while KX is the rate

$\frac{dX}{dt}$ **= input – output** **XBME**

→ In IV Bolus the input is instantaneous (no input over time).

So the rate of change is the elimination rate.

Rate of elimination = dX/dt = -KX

- X = Xo e^{-Kt} (Xo is the initial amount/dose)
  C = Co e^{-Kt} (Co is the initial concentration)
  Vd = Xt / Ct
  ln Cp = ln Co – Kt
  log Cp = log Co - $\frac{Kt}{2.303}$

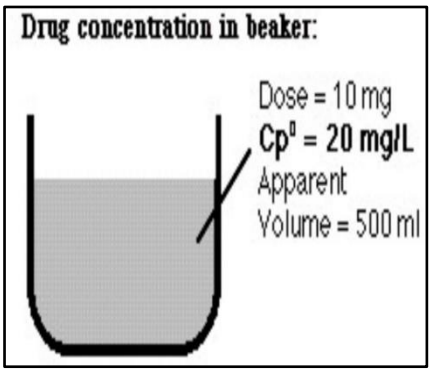
- So the amount of drug in the whole body is given by the equation:
  Xt = Xo e^{-Kt}
  - Xt represents the drug <u>amount</u> at a specific time, Xo is the <u>initial amount</u> (dose), and e^-kt shows the exponential decline over time.
  - Measuring the <u>total drug amount</u> in all tissues is difficult, so we use <u>blood concentration</u>, as blood is easy to sample and analyze. While urine or CSF can be used, blood is the most common sampling pool.
  - To calculate the total drug amount from blood concentration, we need to relate concentration (Amount/Volume) to an appropriate volume:

Volume of Distribution

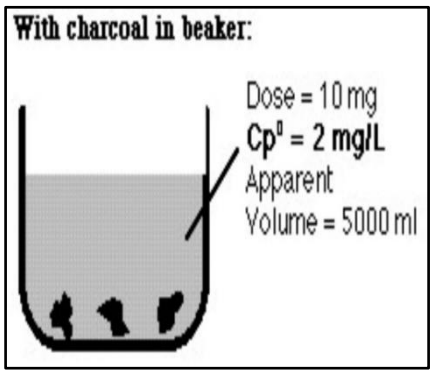
- The **apparent volume of distribution (Vd)** is a mathematical concept that links the amount of drug in the body to its concentration in plasma, the volume of distribution can be much larger than the actual body volume, but it is never smaller than the volume of blood or plasma.

$$V_d = \frac{\text{AMOUNT of drug in the body}}{\text{CONCENTRATION in plasma}}$$

- ***Factors affecting drug distribution:***
  - ***Rate of distribution*** *(Number of compartments)*
    - ✓ Membrane permeability
      - Lipid Solubility
      - pH -pKa (pH-partition theory for ionizable molecules)
    - ✓ Blood perfusion of organs and tissues
  - ***Extent of Distribution*** *(Volume of distribution)*
    - ✓ Plasma protein binding
      - If the drug is highly bounded to plasma proteins then it will mainly be in the blood (Low Vd)
    - ✓ Intracellular binding
      - If the drug is highly bounded to intracellular macromolecules then it will mainly stay in the tissues (high Vd)



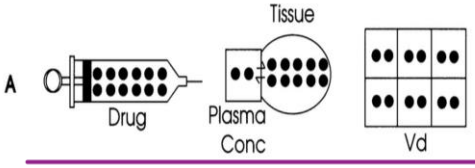
- How can we know the volume of a certain solution? (you only know it's absorption and added amount of the drug) Simply, we draw calibration curve (a relation that helps in obtaining the concentration from the absorption) So from calibration curve we obtain the conc. as 20 mg/L Now we have both conc. and amount (from the question it's 10 mg) now we can calculate the volume
- Volume = (amount/ conc.) = 10/20 = 0.5 L = 500 ml



- Same solution, same added amount of drug, but here we add charcoal molecules ! (Charcoal has the ability to adsorb drug molecules hence decreasing real conc. of drug in the solution) So we will end with different value of conc.= 2mg/L The amount is 10 mg and the conc. is 2 mg/L
- Volume = (amount/conc.) =10/2 = 5 L = 5000 mL

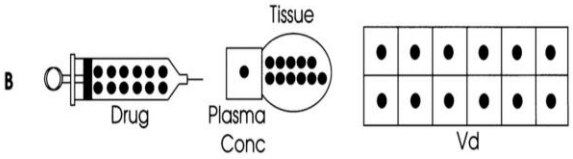
- Even though the same drug amount and solvent volume were used, the calculations showed a **much larger volume**. This is because the drug moved from the solution to the charcoal, increasing the apparent volume (the volume increases if the drug prefers to "move out"). Similarly, in the body, if the drug **prefers to be distributed into tissues** rather than stay in the blood, its concentration in the blood decreases, and the volume of distribution (Vd) increases. This doesn't reflect actual blood or organ volumes but rather the drug's distribution pattern, hence the term "volume of distribution."

- **Example**: we give same dose of 3 drugs (A,B,C) all of them are given in 12 units:



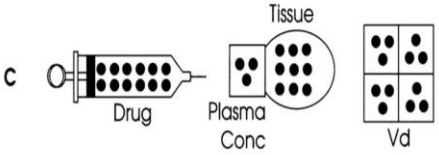
For drug A, the concentration in blood plasma is 2 units, meaning most of the drug (10 units) has moved to other tissues. Since each 2 units occupies a volume equal to the blood volume, the total volume occupied by the drug is 6 times the blood volume.

Vd = Amount/Conc = **12** units / **2** units/blood volume = 6 * blood volume.



For drug B, the plasma concentration is 1 unit, meaning the other 11 units have gone to other tissues. Since 1 unit occupies a volume equal to the blood volume, the total volume occupied by the drug is 12 times the blood volume.

Vd = Amount/Conc = **12** units / **1** unit/blood volume = 12 * blood volume.



For drug C, the plasma concentration is 3 units, meaning 9 units have gone to other tissues. Since 3 units occupy a volume equal to the blood volume, the total volume occupied by the drug is 4 times the blood volume.

Vd = Amount/Conc = **12** units / **3** units/blood volume = 4 * blood volume.

  - Each of these units occupies a volume equal to the blood volume. Since it's difficult to directly measure the drug in the organs, we observe how the drug is distributed in the plasma and assume that the blood represents the other organs. So, if there are 2 units in the blood, it means the other 2 units will distribute similarly across the rest of the body.

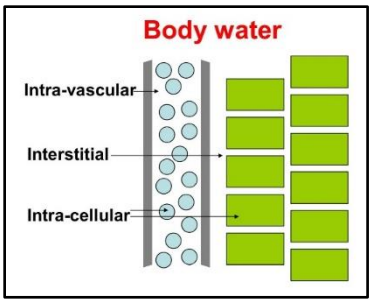
- ***Volume of Distribution:***

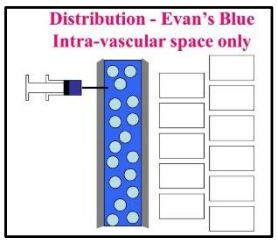
Erythropoietin	5 L	0.07 L/kg*
Warfarin	8 L	0.12 L/kg*
Phenytoin	45 L	0.63 L /kg*
Digoxin	500 L	7 L /kg*
Amiodarone	5000 L	70 L /kg*
Chloroquine	15000 L	215 L/kg*
Quinacrine	35000 L	500 L/kg*

*Distribution Coefficient

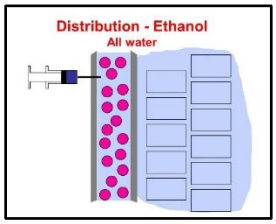
  - Examples: Volumes of distribution for some drugs in young 25 year adult person 70 kg (remember: volume of blood ~ 5 L)

Drug	Notes	Vd	Distribution Coefficient (Vd/body weight)
Erythropoietin	Large protein can't leave the blood easily	5 L, almost equal to blood volume	5/70 = 0.07 L/Kg
Warfarin	Highly bounded to plasma proteins (99%)	8 L	8/70 = 0.12 L/Kg
Digoxin	Highly bounded to muscles	500 L	500/70 = 7 L/Kg
Quinacrine	Highly distributed to the tissues	35 000 L	35 000/70 = 500 L/Kg

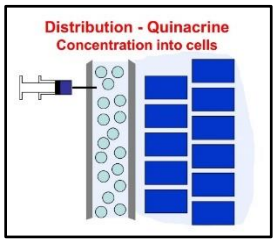




- **Evan's blue** is a contrast media that stays in the blood so we noticed that only intravascular space is colored. While interstitial and intracellular areas are not colored at all (not even light color). This means that Vd value is equal to blood volume.



- **Ethanol** is water miserable so it distributes in same concentration to intravascular area(1), interstitial (2) and intracellular area(3) It's Vd will be equal to water volume in the body (around 60% of adult body volume).



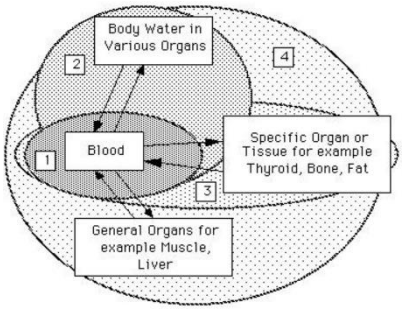
- **Quinacrine** mainly concentrates inside the cells (if you notice the color is strong intracellularly and very light intravenously + interstitially) *Vd = how much volume do I need to dilute intracellular concentration to reach blood concentration? (Because we take samples from the blood).

- **Volume of distribution:**
  - A measure of the <u>tendency</u> of a drug to move out of the blood plasma to some other site.
  - If we know the volume of distribution we can convert the amount of the drug in the body to plasma concentration.
  - Amount (Xo) /Volume of distribution (Vd) = Plasma Concentration (C).
  - $X = Xo\ e^{-Kt}$
    $C = Co\ e^{-Kt}$
    Vd = Xt / Ct

- **Distribution coefficient:**
  - It's a measure of the <u>volume of distribution</u> for <u>each kilogram</u> of the body.
  - We calculate it by <u>dividing the volume of distribution</u> by <u>body weight</u> (important in **individualizing** the doses for patients).
  - **Example:** Digoxin has a volume of distribution of 500 L if we give it to a 70 kg patient then the distribution coefficient will be?
    500/70 = 7 L/Kg, which means that each kilogram of this patient has a volume of distribution equal to 7 L, again this is not a real value.

- So, the **Vd (volume of distribution)** value tells us **where the drug will likely go**. If the Vd is low, it means the drug prefers to stay in the blood, while if it's high, it indicates the drug tends to distribute outside the bloodstream into tissues.
- **Why did we even start talking about Vd?**
  - Remember, our main goal is to determine the total amount of drug in the body. Since measuring it in all organs is difficult, we estimate it by measuring drug concentration in blood and use Vd to link the total amount to this concentration.
  - To calculate Vd, we use the formula: **Vd = Xo / Co.**
  - We prefer to calculate at time zero because it's the only moment when the exact drug amount (X) is known, equal to the administered dose. After that, the drug distributes throughout the body, making the exact amount harder to determine.

Patterns of Vd



Relationship Between the Extent of Distribution and Vd in a 70 kg Normal Man

Vd, L	% Body Weight	Extent of Distribution
5	7	Only in plasma
5-20	7-28	In extracellular fluids
20-40	28-56	In total body fluids
>40	>56	In deep tissues; bound to peripheral tissues

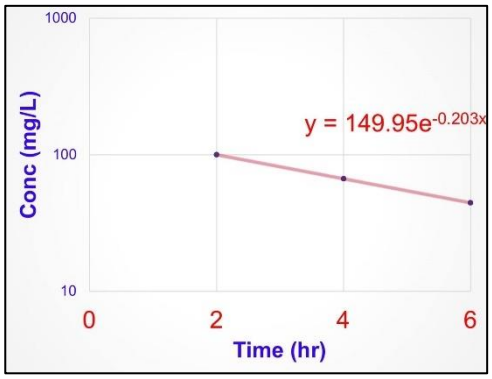
- ***The benefits of knowing the Vd include:***
  - ✓ **Determining the correct dose for administration:**
    For example, if I want to give a patient a dose of digoxin to achieve a concentration of 0.6 ng/mL, how much of the drug should I administer to reach this concentration?
    Using the formula: $Vd = X_0 / C_0$
    Given: Vd = 500 L and $C_0 = 0.6$ mcg/L, we calculate:
    $X_0 = 500\ L * 0.6\ mg/L = 300$ micrograms
  - ✓ **Vd indicates where the drug is located in the body:**
    For instance, if someone has taken a high dose of a drug and we need to perform dialysis to remove it, Vd helps us determine if dialysis will be effective. If the Vd is high, it means the drug is primarily in the tissues rather than in the blood, so dialysis may not be very useful for removing it.

- **Questions:**
  - The volume of distribution equals _____ divided by initial drug concentration:
    A) Clearance
    B) Initial drug concentration
    C) Half-life
    D) Dose

    Answer: D) dose

- A dose of 1000 mg of a drug is administered to a patient, and the following concentrations result at the indicated times below. Assume a one-compartment model.

Plasma Conc (mg/L)	Time after dose (hr)
100	2
67	4
45	6



An estimate of the volume of distribution would be:

A) 10 L.
B) 22.2 L.
C) 6.7 L.
D) 5 L.

Answer: C) 6.7 L.

- If a drug is poorly distributed to tissues. Its apparent volume of distribution is probably:

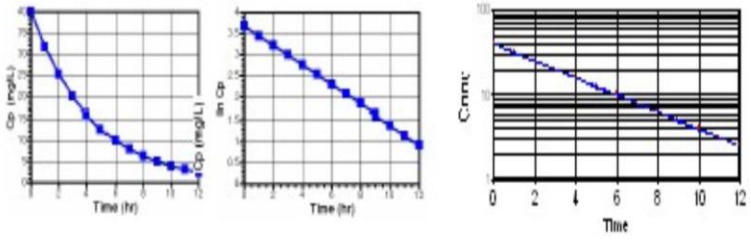
A) large
B) small

Answer: B) small

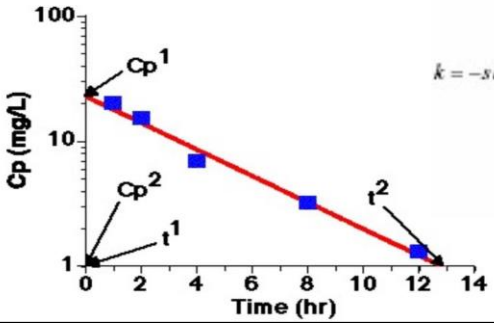
Cp vs. Time Plots

$C = C(0) \cdot e^{-kt}$ $\ln(C) = \ln C(0) - kt$ $\log_{10}(C) = \log_{10} C(0) - \frac{k}{2.303} t$

Cp vs. Time | Ln *Cp vs.* Time | Semi-log Plot *Cp vs.* Time



Cp versus Time Data					
Time (hr)	1	2	4	8	12
Cp (mg/L)	20	15	6.8	3.2	1.3

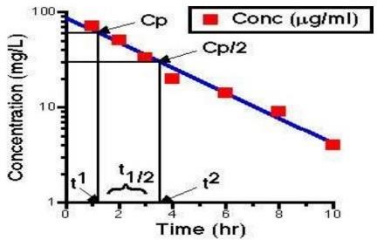


$$k = -slope = -\frac{\ln C(2) - \ln C(1)}{t(2) - t(1)}$$

$$= -\frac{\ln 1 - \ln 21}{12.8 - 0} = 0.253 hr^{-1}$$

Elimination half-life ($t_{0.5}$)

- Definition: is the time for any concentration to drop to its half.
  - It is a secondary parameter :
  - The elimination half-life is dependent on the ratio of CL and VD.
    t0.5= 0.693/k
  - Unit: time (min, h, day) Elimination half-life (t1/2)



  - What is the importance of half-life?
    Shown in the next example:
    A certain drug is given in an initial concentration of (10 mg/L)
    After the first half-life, the concentration is 5 mg/L
    After the second half-life, the concentration is 2.5 mg/L
    After the third half-life, the concentration is 1.25 mg/L
    After the fourth half-life, we concentration is 0.625 mg/L

A) What is the time needed to reach a concentration = 2 mg/L?
We will reach conc. = 2 after more than two half-lives but less then 3 half-lives Because the concentration after two half-lives is 2.5 while the concentration after three half-lives is 1.25

B) If the minimum effective concentration was 1 mg then what is the duration of action?
Remember: duration of action is the period of time at which the concentration is above the minimum effective concentration.
The duration of action continues for more than 3 half-lives but less than four.

Fraction of Dose Remaining

n : the number of $t_{1/2}$ elapsed after a bolus IV dose

$n = t/t_{1/2}$ Fraction of dose remaining = $(1/2)^n$

Number of $t_{1/2}$ elapsed (n)	% Dose remaining	% Dose eliminated
1	50	50
2	25	75
3	12.5	87.5
4	6.25	93.75
5	3.125	96.875
6	1.563	98.437
7	.781	99.22
8	.039	99.61

- ***Summary: What is the importance of half-life?***
  - Half-life tells us the time it takes for the concentration of the drug to reduce by half. This helps us estimate when the drug will be cleared from the body, as with each half-life, 50% of the remaining drug is eliminated.

    Practically, 97% of the drug will be eliminated after 5 half-lives, but theoretically, it will never reach zero because the process is exponential.

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