◉ Sheet ○ Slides

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Pharmacokinetics

Elimination Process:

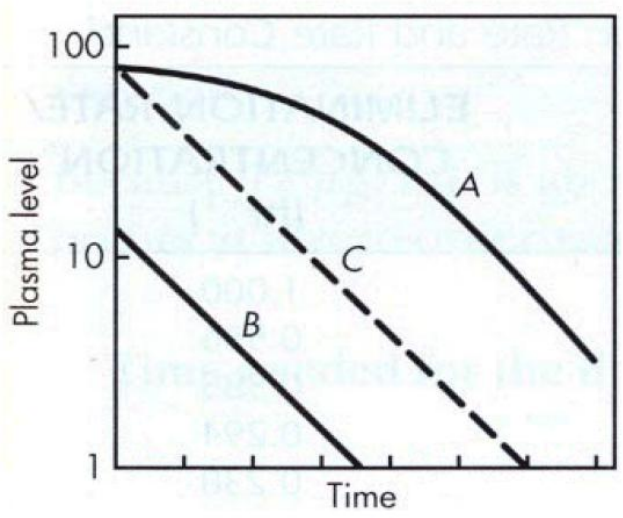
-Types of Elimination Kinetics

First-Order Elimination (Quick Review)

In first-order elimination kinetics, a constant **fraction** of the drug is removed per unit of time, thus whether the dose given is for example, 1000 mg or 100 mg, half of the given dose will be eliminated per unit of time, most drugs follow the first-order elimination kinetics at their therapeutic concentrations.

Zero-Order Elimination

A constant **amount** (NOT fraction) of the drug is removed per unit of time, because the elimination process is **saturated**. Therefore, elimination rate is NOT proportional to the amount of the drug in the body. For example, if the dose given was 10 mg and the rate of elimination was 1 mg/hour, we would need 10 hours to get rid of the drug. In contrast, with first-order elimination which occurs with most drugs, zero-order elimination occurs only with a few drugs (such as: aspirin, phenytoin and ethanol). This is beneficial to prevent the accumulation of drugs in the body, as first-order elimination gets rid of the drug faster because a constant fraction of the drug is removed per unit of time whether the given dose was high or low.



Note that saturation in first-order elimination doesn't happen around the therapeutic concentration, but with much higher doses, saturation could happen.

This is similar to enzyme-kinetics, where at high concentrations of the

substrate, the enzyme is saturated and the plot is said to be zero-order.

As we have learned before, the semi-logarithmic plot (where the y-axis is logarithmic and the x-axis is linear) for first-order elimination drugs is **linear** (plot C). For zero-order elimination drugs, the semi-log plot is **curved down** (plot A). For plot A, we noticed that at high concentrations, the slope is low (slow elimination), which means that the reduction in the plasma concentration of the drug (relatively) is low. At low concentrations (below the saturation level), the plot becomes linear. For example, suppose that saturation happens at 2 mg/L. Below 2 mg/L, the plot is first-order and above 2 mg/L the plot is zero-order.

In first-order elimination kinetics, we have talked about various variables that affect such as the volume of distribution and clearance. These variables are not useful in zero-order elimination kinetics because of the presence of saturation. Instead we use the following equation:

$$Rate\ of\ Elimination = \frac{Vmax \times C}{Km + C}$$

where Vmax is the maximal elimination capacity and Km is the drug concentration at which rate of elimination is 50% of Vmax.

What is the importance of differentiating between zero-order elimination drugs and first-order elimination drugs?

Suppose that we have given a dose of 500 mg of an unknown drug that follows first-order elimination kinetics, expecting that it would give the therapeutic concentration of 15 mg/L. But when measuring the drug concentration, we found that the concentration was 10 mg/L, which means that we need to increase the dose.

The correct dose can be calculated by as follows:

$$Correct\ Dose = \frac{Therapeutic\ Concentration}{Measured\ Concentration} \times Original\ Dose$$

Thus, the correct dose would be 750 mg.

On the other hand, with zero-order elimination drugs, this extra 250 mg might give us an out of proportion concentration which might lead to toxicity, since higher concentrations of zero-order elimination drugs approach to their saturation level, the rate of elimination will no longer be linear, where instead it decreases (this is further demonstrated from the curve A in the figure found on the right), that's why the equation mentioned above is not applicable for zero order elimination.

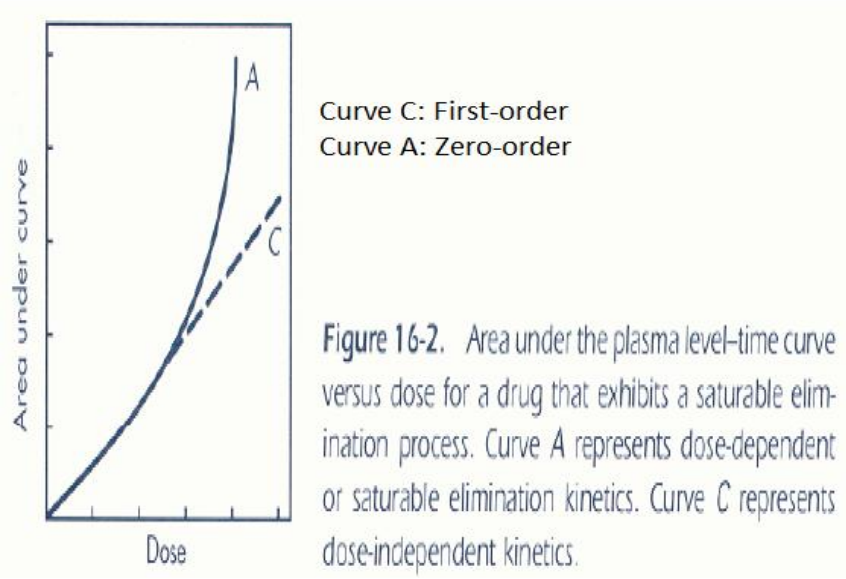


Figure 16-2. Area under the plasma level–time curve versus dose for a drug that exhibits a saturable elimination process. Curve A represents dose-dependent or saturable elimination kinetics. Curve C represents dose-independent kinetics.

*Note: For the reason mentioned above, to predict the correct dose for zero-order elimination drug, we slightly increase the given dose (e.g: from 500mg to 550mg), in order to ensure that the dose hasn't caused any adverse and toxic effects and is maintained in the therapeutic range (it's a trial technique with varying the doses and monitoring the effects, in order to obtain the optimal dose).

Flow-dependent Elimination

It is the elimination that depends on the blood flow to the organ of elimination (mainly the liver), because the organ of elimination is full with enzymes that metabolize these drugs. Rate of elimination is determined by the rate of hepatic blood flow. If we increase the hepatic blood flow, elimination increases, and if we decrease it, elimination decreases. Drugs that undergo flow-dependent elimination are called high-extraction ratio drugs. The difference between the IV dose and the oral dose for these drugs is large, because the entire dose is going to pass by the liver first and get metabolized, while the IV dose will enter the

systemic circulation directly. Examples on this type of drugs include morphine, lidocaine, propranol and verapamil.

Half-Life (t½)

The time required for the amount of the drug in the blood or the plasma to drop by **50%**. The **fraction** of the drug removed is constant in first-order kinetics, and does not depend on the amount of the drug. After 4 half-lives pass, most of the drug will be eliminated from the body (Notice from the table on the right.

Number of half-lives	% of drug removed
1	50
2	75
3	87.5
4	93.75

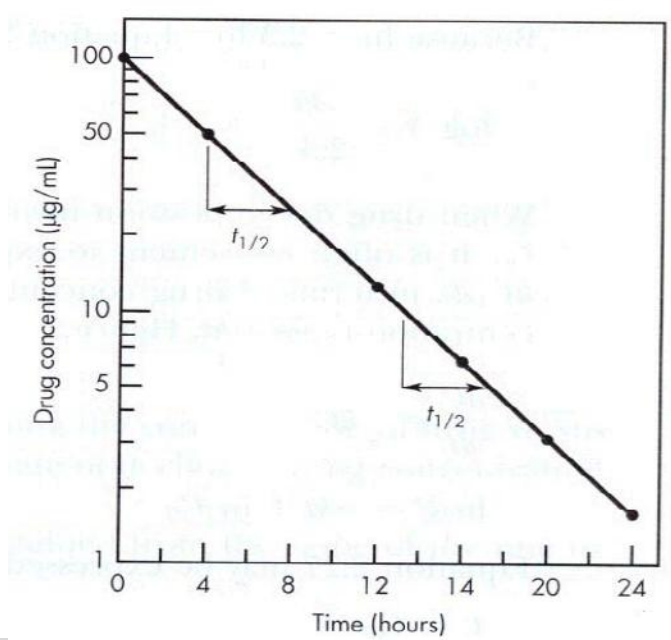
How do we calculate the half-life from a graph?

In first-order elimination kinetics, the semi-log plot is linear. We take one concentration and its corresponding time reading. Then we go down to half this concentration and its corresponding time reading. The difference between the time readings of the two concentrations is the half-life of the drug. In the graph below, the time reading at the concentration 100 is 0 hours. The time reading at half that concentration (50) is 4 hours. The difference is 4, which is the half-life of the drug.

In zero-order elimination kinetics, the half-life is not constant, but is related to the concentration of the drug. The higher the concentration, the longer the half-life of elimination is and vice versa.

The half-life of a first-order elimination drug can be calculated theoretically using this equation:

$$k \times t½ = 0.693$$



The half-life is related to the volume of distribution and clearance by the following equation:

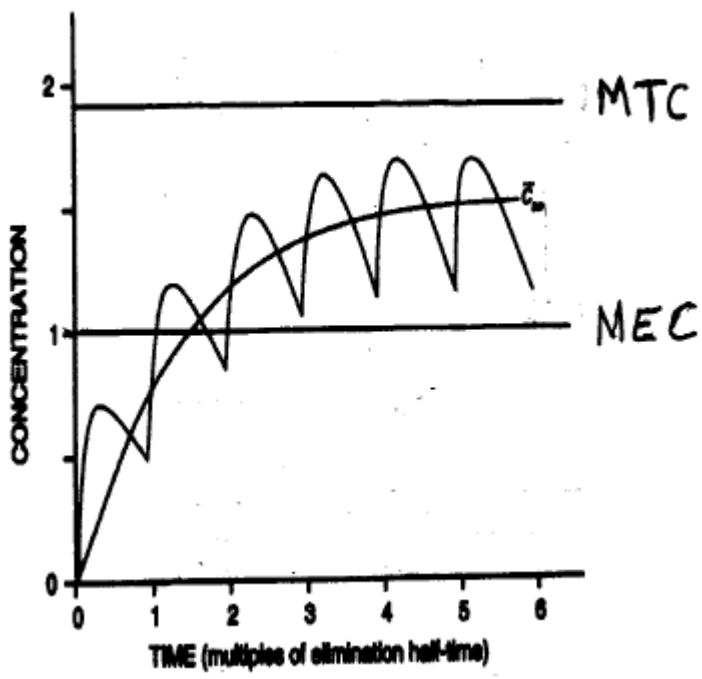
$$t½ = .693 \times \frac{Vd}{CL}$$

By substituting k in the above equation we get:

$$CL = k \times Vd$$

Steady-State

Steady-state occurs when the rate of drug administration equals the rate of drug elimination. Steady-state is achieved with repeated drug administrations and not with one dose, where it leads to a roughly constant concentration of the drug in the body within therapeutic range. It is achieved after approximately 4 half-lives.



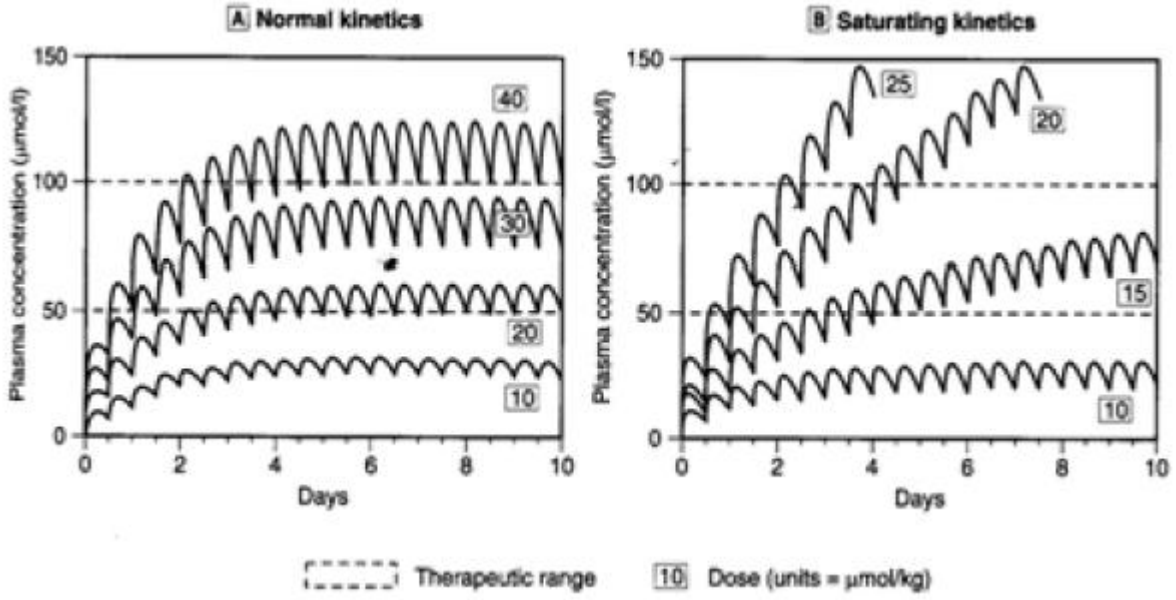
MEC = Minimum Effective Concentration

MTC = Minimum Toxic Concentration

How do we achieve a steady-state?

Suppose that we give an oral dose to reach a concentration of 1 mg/L, after 1 half-life passes, the concentration decreases by 50% to reach .5 mg/L. Then we give another oral dose, and the concentration increases to 1.5 mg/L. Another half-life passes, decreasing the concentration to .75 mg/L. Then we give yet another dose to increase the concentration up to 1.75 mg/L. The next half-life passes which decrease the concentration to .875 mg. With continuous drug administration each half-life, the drug concentration approaches a steady-state concentration of 2 mg/L.

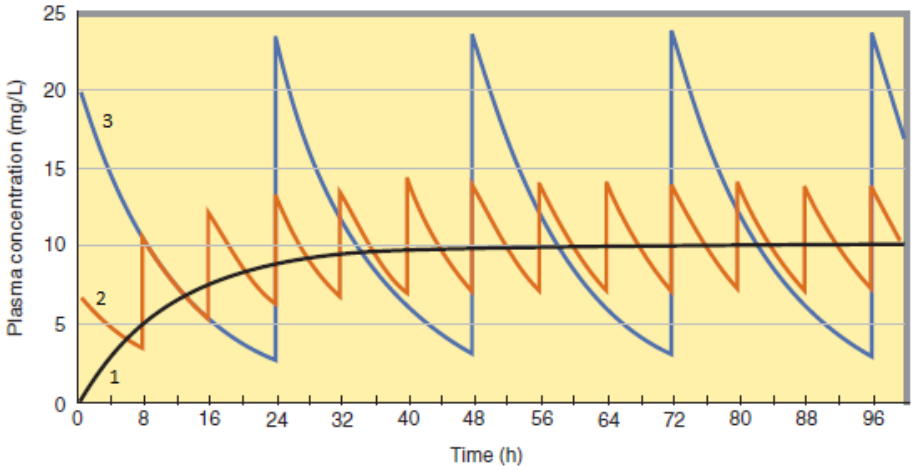
Note that our aim during drug therapy is to attain a steady-state drug concentration (Css) within the **therapeutic range** (neither sub-therapeutic nor toxic). We want the crest (peak) and the trough (base) to be within the therapeutic range.



Looking at the graph above (left), we can see 4 steady-states. The space between the two dashed lines represents the therapeutic range. Counting from below, curve number 3 represents the best situation, because the peak and the trough are within the therapeutic range. Curve number 4 is toxic while curve number 1 is

sub-therapeutic. Curve number 2 is sub-therapeutic on the minimal concentration, thus it's not as good as number 3.

The right graph represents zero-order elimination drugs, where a steady-state cannot be reached except at low concentrations which are not beneficial because they are sub-therapeutic.



The graph above show 3 curves. Curve number 1 represents a dose given by IV infusion (drip), it's smooth with no fluctuations, achieving the desired therapeutic steady-state concentration of 10 mg/L. Curve number 3 represents a dose given orally once a day. It fluctuates between toxic concentrations and sub-therapeutic concentrations, so the patient occasionally suffers adverse effects or no effects (sub-therapeutic) in each drug administration. Curve number 2 represents a dose given orally every 8 hours. It achieves a steady-state within the therapeutic range with minor fluctuations.

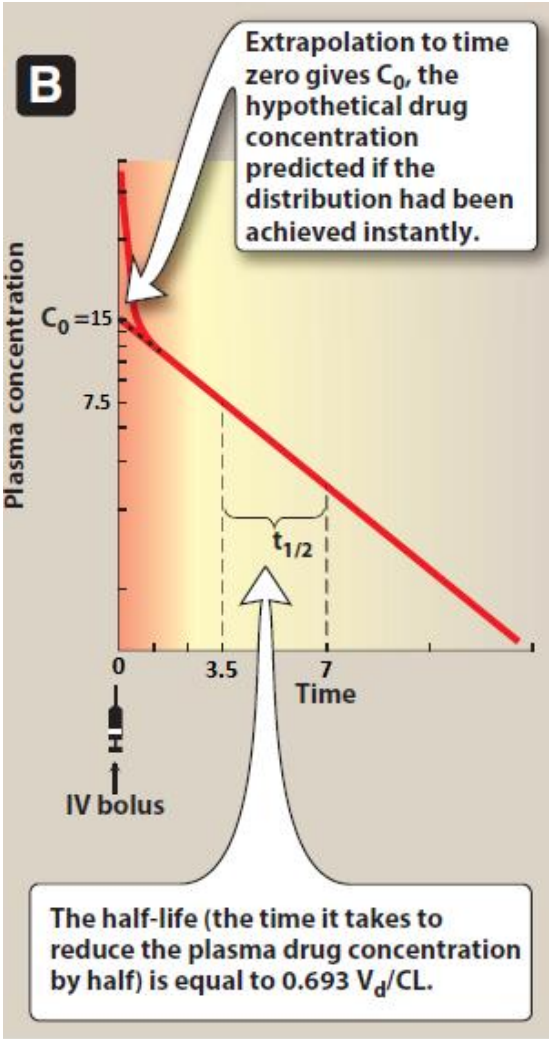
This is the reason why some drugs are given once a day and others are given two or three times a day. A drug given once a day should have a peak concentration below the toxic concentration and a trough above the sub-therapeutic concentration.

Loading Dose (LD)

To reach a steady-state, we need 4 half-lives. A drug with a half-life of 1.5 days such as digoxin, would need 6 days to reach a steady-state. Amiodarone, an antiarrhythmic medication having a half-life of about 2 months, would need 8 months to reach a steady-state. We cannot wait this long, especially when the patient is in a critical condition. To solve this problem, we give the patient a loading dose that raises the concentration of the drug almost immediately to the target concentration. We calculate the loading dose using the following equation:

$$LD = Vd \times Css$$

After that we have to maintain this dose (maintain a steady-state), by compensating for the amount of the drug lost by elimination. We achieve this by giving a maintenance dose.



Maintenance Dose (MD)

In order to maintain a steady-state, we need to adjust the dose so that the rate of drug administration is equal to the rate of drug elimination. We calculate the maintenance dose using the following equation:

$$MD = CL \times Css$$

Case Study

A volunteer was administered a single 400 mg dose intravenously. Serial blood samples were taken to measure the drug concentration in the plasma. A semi-log plot was constructed as the graph shows.

The beginning of the plot is not linear, because the dose doesn't distribute instantly. This phase is

called the distribution phase, and doesn't appear when the drug is given orally because absorption occurs slowly, therefore distribution and absorption occur simultaneously.

- **Calculate the apparent volume of distribution.**

$$Vd = \frac{Dose}{Concentration\ at\ time\ zero}$$

The concentration used in the equation is the extrapolated (hypothetical) zero-time concentration if the distribution of the drug happened instantly. In reality, we cannot have zero-time concentrations.

*Note: In order to obtain concentration at zero time, it cannot be measured experimentally (since its not realistic and , so its calculated hypothetically by extrapolating the curve when it becomes linear in a semi-log plot until it crosses the y-axis (concentration axis), the value read with the extrapolated plot has crossed is **C_0** (zero-time concentration)

Vd = 400/15 ≈ 25 L

- **What is the half-life of elimination of the drug?**

3.5 hours.