PHARMACOLOGY

بسم الله الرحمن الرحيم

MID – Lecture 3

Pharmacokinetics (Pt.2)

﴿ وَإِن تَتَوَلَّوْا يَسْتَبْدِلْ قَوْمًا غَيْرَكُمْ ثُمَّ لَا يَكُونُوا أَمْثَالَكُم ﴾

اللهم استعملنا ولا تستبدلنا

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فريق دوبامين العلمي - THE SCIENTIFIC TEAM OF DOPAMINE -
APPROVED
0503201
Lecture 3

Before we start.

Just to set matters right. In this lecture, we will be dealing with abstract and basic concepts and relationships between Pharmacokinetics parameters and variables. Hence, there will be a handful of mathematical equations to come across and a bunch of visuals to demonstrate. For now, try to comprehend this subject conceptually and do not worry about the calculations, as Doctor samar said, in the coming lecture we will tackle many problems and challenges to assess our understanding.

Key Pharmacokinetic Parameters

- Half-life (t½): Time it takes for the plasma concentration of a drug to reduce by half. The reduction in concentration is due to clearance.

Assume Drug X has a half-life of 10 minutes, and is prescribed with a dosage of 50 mg. After 10 minutes, the concentration of the drug in the plasma will reduce to 25 mg (50% of the original amount). Another 10 minutes later, the concentration will reduce further to 12.5 mg, and this process continues, halving with each half-life. A drug's half-life is typically determined during clinical trials and is relatively fixed.

- Clearance (Cl): The rate at which a drug is removed from the body

The elimination or removal of the drug is also a gradual process

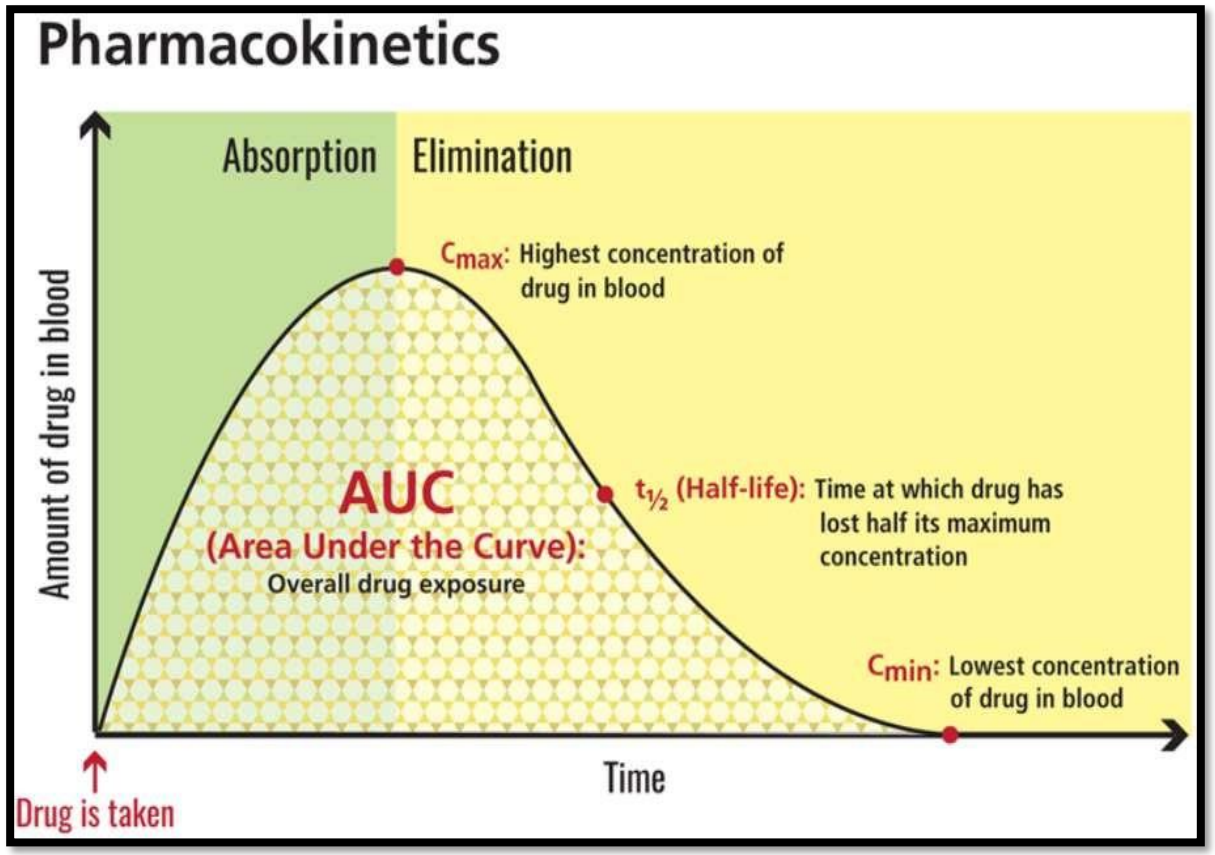
- In **multiple-dose** drug administration or **continuous IV infusion**, the drug reaches a steady-state concentration (Css) over time. This occurs when the rate of drug administration equals the rate of drug elimination, meaning that further drug administration will no longer increase the plasma concentration.
- Steady-state is typically achieved after **4-5 half-lives**. After reaching this point, maintaining the same dosing schedule will keep the plasma concentration stable.
- However, increasing the dose or frequency beyond this can lead to elevated drug levels, causing toxicity and side effects. This phenomenon does not occur with single-dose administration, as the drug is eliminated before it has time to accumulate.
- Further details will be discussed in the next slide.

Single-dose administration

Further elucidation

When a drug is administered, only a portion of it is absorbed into the bloodstream due to various factors, with the exception of IV administration, which results in 100% absorption. This fraction of the drug that enters the bloodstream is referred to as bioavailability (to be discussed in detail later). The drug is gradually absorbed, and its plasma concentration increases until it reaches the maximum concentration. At the same time, the drug is continuously being eliminated, either by the first-pass effect in the liver (for orally administered drugs) or through the kidneys. As the concentration declines, the time it takes for the plasma concentration to drop by 50% is called the half-life. This process continues until the drug concentration falls below the therapeutic level and is eventually cleared from the plasma.

More details will be provided in the upcoming slides.



Take a closer look at the graphs below to obtain better understanding.

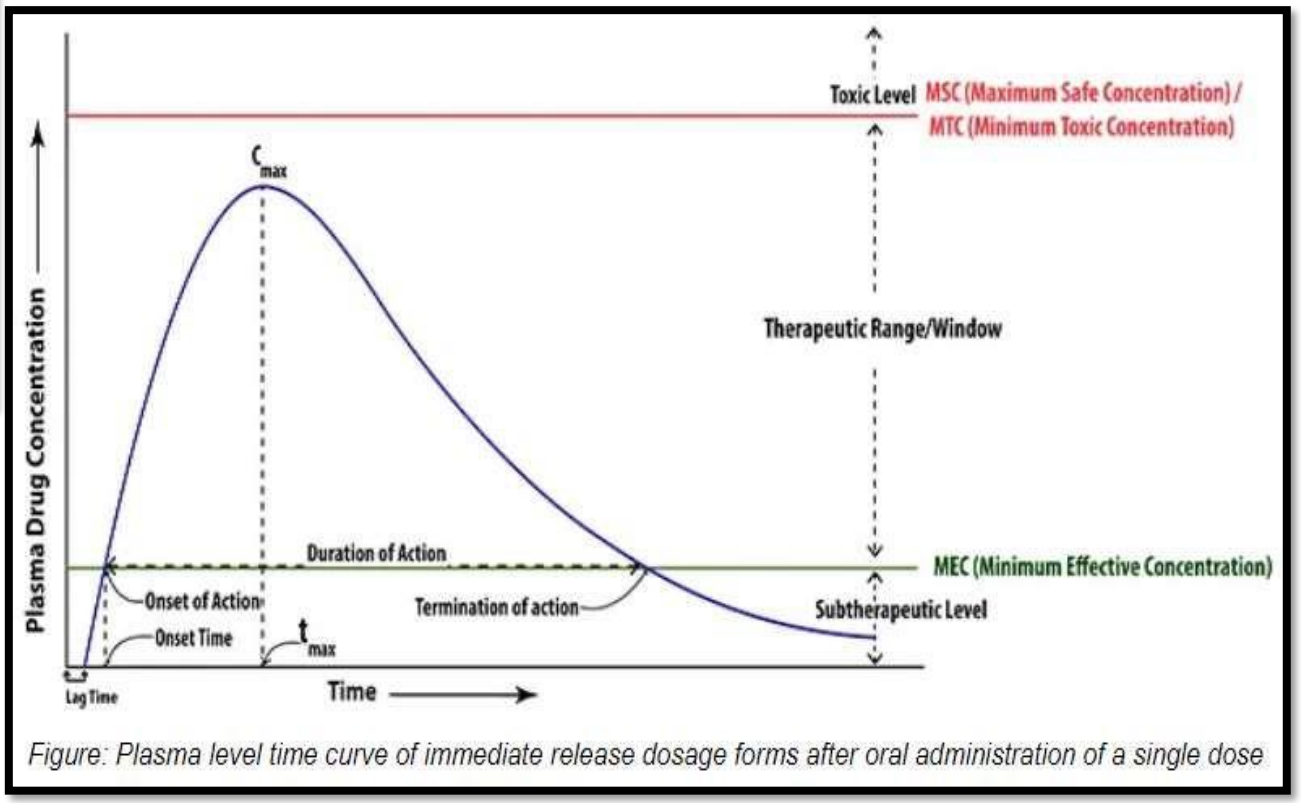


Figure: Plasma level time curve of immediate release dosage forms after oral administration of a single dose

Continuous infusion of the drug

Further elucidation

In continuous drug infusion, there will be continuous accumulation of the drug, over time and after 4-5 half-lives elapsed, the steady state is achieved, and plateau is established. That is, any further drug administration will not increase plasma conc. Of the drug. Therefore, the blood is said to be saturated. Once infusion ceases, a sharp drop in the drug conc. Takes place.

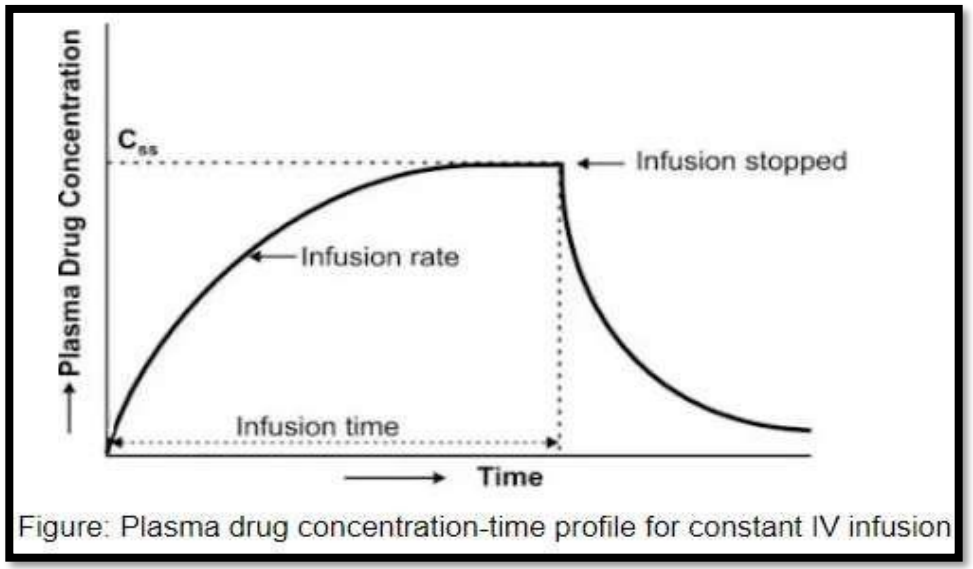


Figure: Plasma drug concentration-time profile for constant IV infusion

Multiple doses administration

Further elucidation

In multiple drug administration, Drug conc. Fluctuates up and down during successive administration of the designated doses.

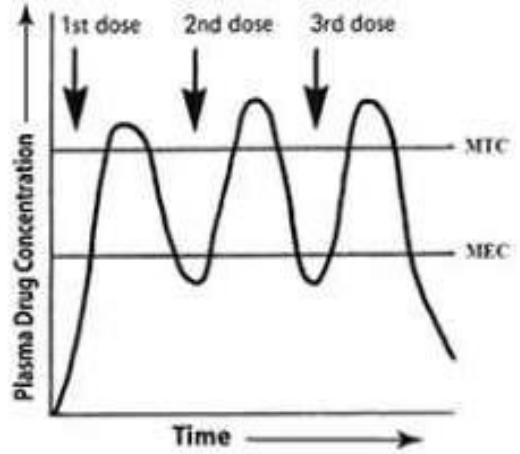


Figure: Drug concentration vs time graph of multiple doses of immediate-release dosage forms

- Bioavailability (F): The proportion of the drug that reaches systemic circulation.

This variable is related to the absorption and route of administration, For example: Drug taken by IV is 100% absorbed into the blood stream. Therefore, Bioavailability in other routes of administration is always a ratio of IV.

- Volume of distribution (Vd): The apparent volume in which the drug is distributed.

- Drugs distribute into various body fluid compartments, including plasma, extracellular fluid, and intracellular fluid.
- A drug that distributes widely across all these compartments will have a high volume of distribution (Vd), compared to a drug that is restricted to the plasma or cannot enter the interstitial fluid.
- As a result, drugs with a high Vd often require larger dosages to achieve the desired plasma concentration.
- Several factors influence Vd. For example, low molecular-weight drugs tend to diffuse easily into the extracellular fluid (ECF), leading to a higher Vd.
- In contrast, factors such as protein binding can lower Vd. Drugs that bind extensively to plasma proteins, like albumin, are trapped in the blood and are less able to enter the interstitial or intracellular fluid, resulting in a lower Vd.

Half-life (t1/2) Calculation

The kidneys contain nephrons that filter blood, retaining plasma proteins while allowing smaller molecules and toxins to pass through. The amount of fluid reabsorbed depends on the body's hydration status; when water levels are low, the kidneys increase water reabsorption. The glomerular filtration rate is steady in healthy individuals.

- **Content**:
  - Formula: $t_{1/2} = 0.693 \times Vd/Cl$

Clearance (Cl): The removal of a drug from the body, which can occur through pathways such as the kidneys (via glomerular filtration).
Drugs often need to be metabolized into water-soluble forms to be excreted by the kidneys. If the drug remains lipophilic, it may be metabolized and excreted in bile (and eliminated in feces).

  - Explanation of each variable.
  - Example calculation of half-life with real data.
- **Visuals**: A graphical representation of drug concentration falling over time, highlighting the half-life

Clearance is measured by analyzing urine samples and knowing how much of the medicine is left.

Volume of Distribution (Vd) Calculation

- **Content**:
- Formula: Vd=Dose/C0
- Explanation: Where C_0 is the initial drug concentration.
- Example calculation with practical data.
- **Visuals**: Illustration of how drugs are distributed into body compartments.

We use this to understand how the initial concentration decreases with each half life. C_0 is the initial concentration and after the first half life it reduces to half of C0. With each subsequent half-life, the concentration continues to halve, following an exponential decay pattern

Clearance (Cl) Calculation

Even when a drug is administered intravenously (IV), accumulation in the blood does not reach 100% instantly. Although IV administration delivers the drug directly into the bloodstream, it takes time for the drug to distribute throughout the body and reach its maximum concentration (C_{max}).

- Content:
- Formula: Cl=Dose/AUC
- Explanation: AUC (Area Under the Curve) represents the total drug exposure over time.
- Example calculation with a plot showing the AUC.
- Visuals: A drug concentration vs. time graph with the AUC shaded.

Clearance Example:

- For a 14-hour operation, I need to keep the drug concentration in the blood at a steady level for a long time. The drug I'm using has a half-life of 1 hour, which means half of the drug is cleared from the body every hour. To maintain a stable concentration, I give the drug continuously through an IV. After about 4 to 5 hours (4 to 5 half-lives), the drug levels in the blood become stable and reach what's called a "steady-state" or plateau. At this point, the amount of drug going in equals the amount being cleared, so the concentration stays constant.
- Even if the operation lasts 10 or 14 hours, the drug concentration will remain stable after those first 5 hours. Once the operation is done, I stop the infusion. After stopping, the drug is cleared from the body in a predictable way: first 50% is cleared, then 25%, then 12.5%, and so on, but it never reaches exactly zero.

Bioavailability (F) Calculation

When a drug is administered orally, not all of it gets into the bloodstream because of processes like digestion and first-pass metabolism. IV administration delivers the drug directly into the bloodstream, so it is 100% bioavailable. By comparing the AUC of oral administration to the AUC of IV administration, you can calculate the bioavailability of the drug when taken orally.

- **Content**:
- Formula: $F = AUC_{oral} / AUC_{IV} \times 100$
- Explanation: Comparing the bioavailability of oral administration vs. intravenous (IV).
- Example calculation with different AUCs.
- **Visuals**: Two AUC graphs side by side (oral vs. IV).

Maintenance Dose Calculation

C_{ss}: Steady-state concentration
Cl: Clearance
F: Bioavailability

C_{ss} (Steady-state concentration) is the concentration at which the drug levels become stable after repeated doses or continuous infusion. At this point, the amount of drug administered equals the amount being cleared from the body. The goal is to maintain C_{ss} by adjusting the dose to match the drug's clearance and bioavailability.

- **Content**:
- Formula: Maintenance Dose=Css×Cl/F
- Explanation: Css is the steady-state concentration of the drug.
- Example calculation.
- **Visuals**: Diagram showing steady-state concentration.

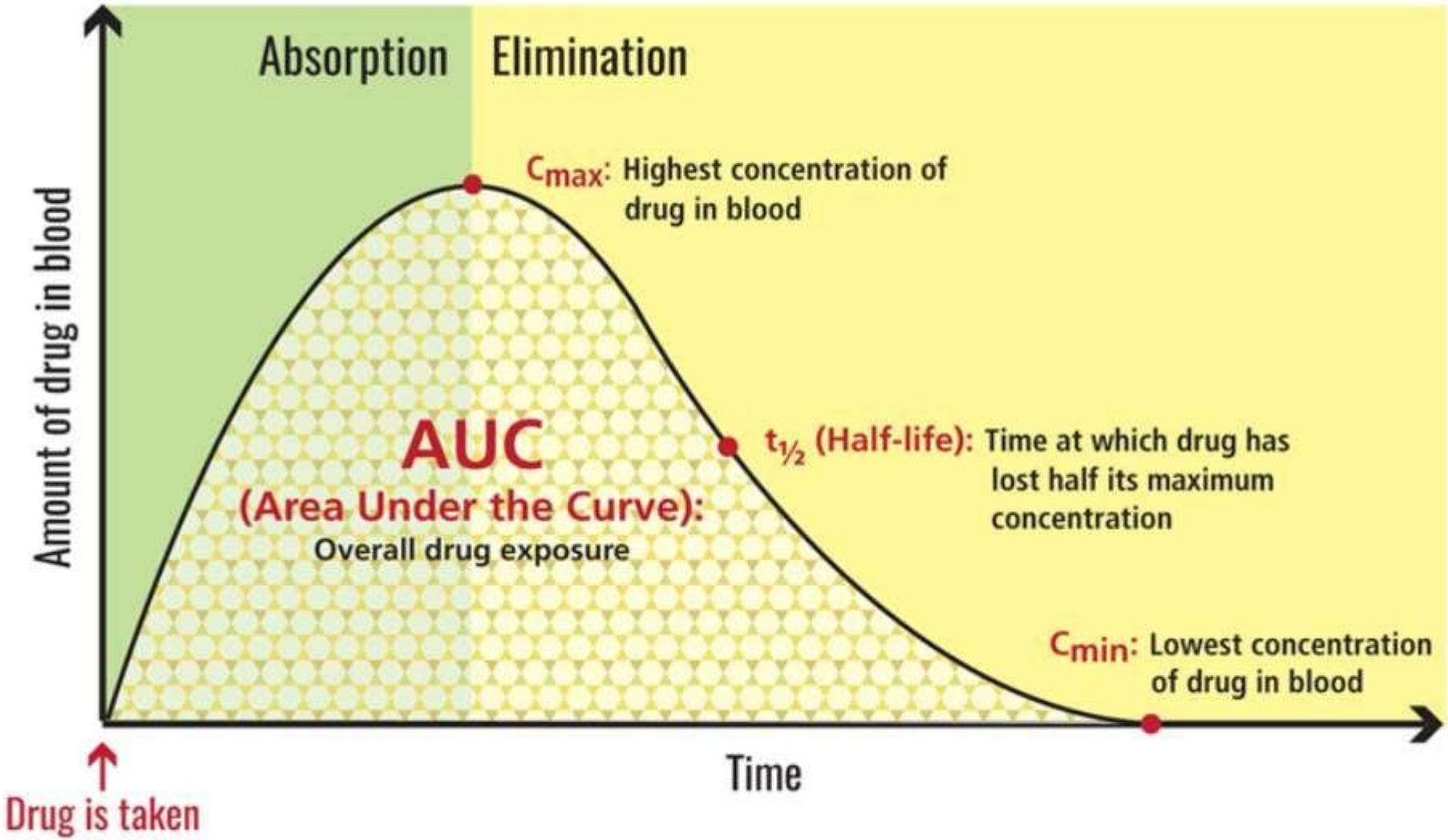
Loading Dose Calculation

- The **loading dose** is used to quickly bring the drug concentration up to the therapeutic (**steady-state**) level. This is often necessary when immediate drug action is required.
- After administering the loading dose, smaller **maintenance doses** are given to keep the drug level steady (C_{ss}).

Css: Steady-state concentration
Vd: Volume of distribution
F: Bioavailability

- **Content**:
- Formula: Loading Dose=Css×Vd/F
- Explanation: Initial higher dose to quickly achieve a therapeutic concentration.
- Example calculation.
- **Visuals**: Graph comparing loading dose vs. maintenance dose over time.

Pharmacokinetics



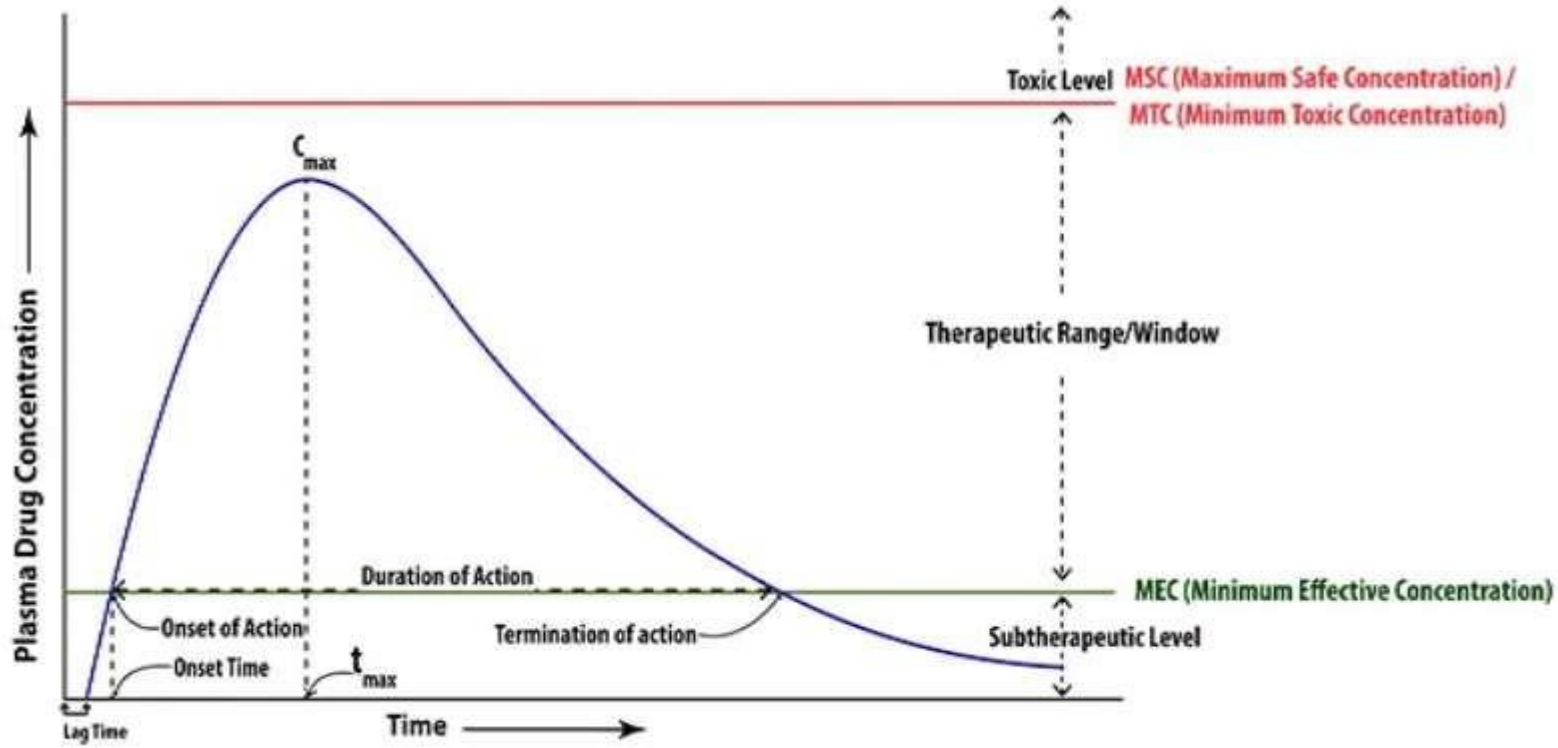


Figure: Plasma level time curve of immediate release dosage forms after oral administration of a single dose

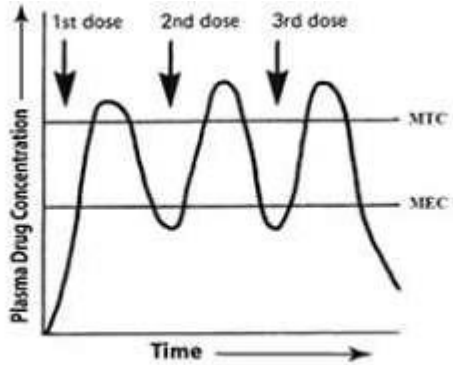


Figure: Drug concentration vs time graph of multiple doses of immediate-release dosage forms

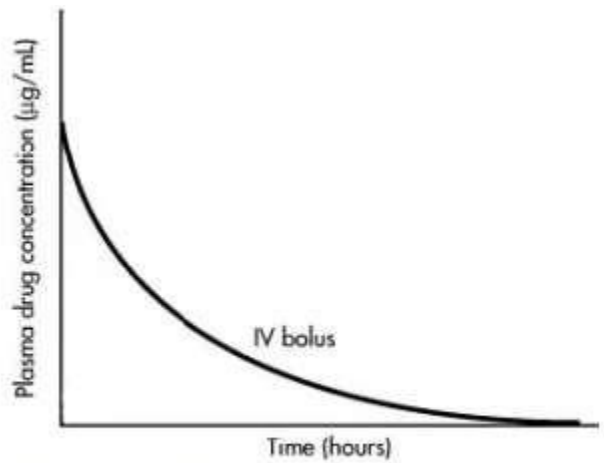


Figure: Plasma level time curve of a single intravenous bolus dose of a drug

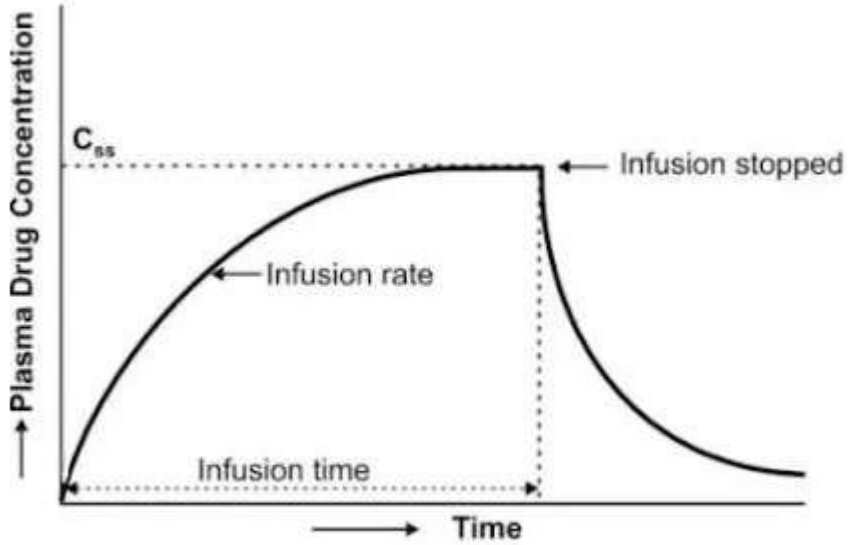


Figure: Plasma drug concentration-time profile for constant IV infusion

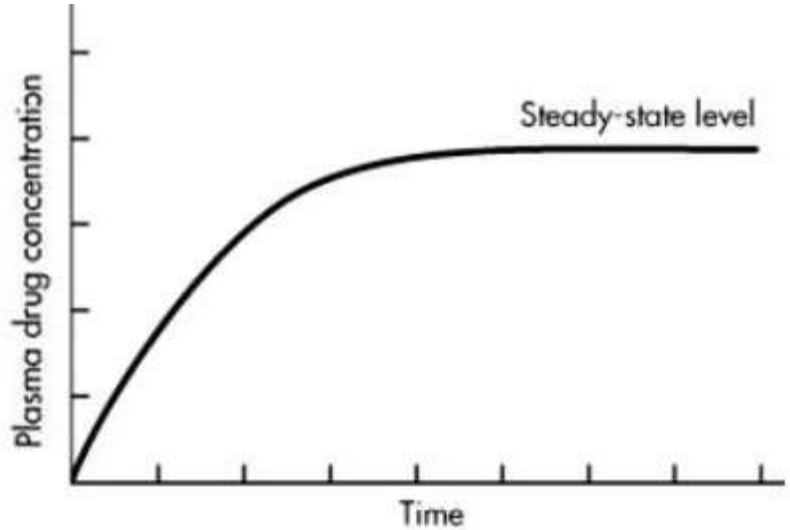
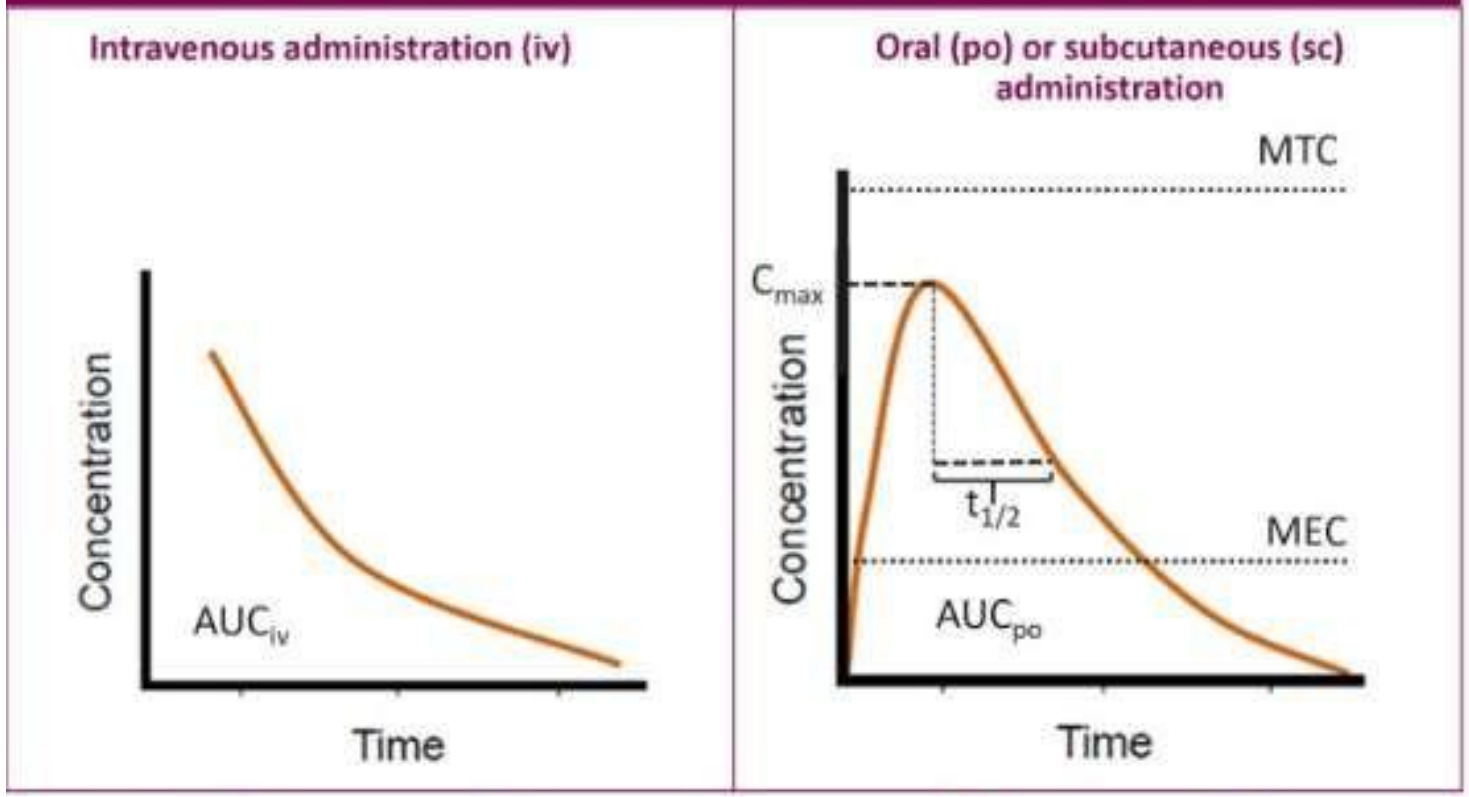


Figure: Drug concentration vs time graph of controlled release / sustained release dosage forms after administration of a single dose

The total area under the curve (AUC) for IV administration represents 100% bioavailability, as the drug enters the bloodstream directly.

IV infusion results in 100% of the area under the curve (AUC) because all of the drug reaches the bloodstream. Oral administration typically results in a lower AUC than IV, often around 75%.

Pharmacokinetic parameters of a plasma concentration time profile



CL	V_d	C_{max}	AUC	$t_{1/2}$	F
• Clearance • Reflects the rate of drug elimination	• Volume of distribution • Measure of the extent of distribution in organs and tissues	• Maximum concentration of drug in plasma	• Area Under the Curve • Describes the total exposure to a drug	• Half-life • The time needed to reach half of drug maximum concentration	• Bioavailability $F = \frac{AUC_{po}/dose_{po}}{AUC_{iv}/dose_{iv}}$

For any other route, the bioavailability is a ratio of the AUC of that route to the AUC of IV administration, which is 100%.

Clinical Relevance

- Dose adjustments: Based on pharmacokinetics, especially in patients with liver or kidney dysfunction.
- Therapeutic drug monitoring: Measuring drug levels in the blood to ensure efficacy and avoid toxicity.
- Drug interactions: How other medications can alter absorption, metabolism, or excretion.

Conclusion

- Summary: Pharmacokinetics helps determine how much of a drug should be administered and how frequently.

- Final Thought: A comprehensive understanding of ADME processes is essential for optimizing therapeutic outcomes and minimizing adverse effects

For any feedback, scan the code or click on it.

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1			
V1 → V2			

Additional Resources:

رسالة من الفريق العلمي:

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References Used:
(numbered in order as cited in the text)

Lippincott Illustrated Reviews, 8th Ed.
Chapter 1