PHARMACOLOGY

بسم الله الرحمن الرحيم

MID – Lecture 5

Pharmacokinetics (Pt.4)

﴿ وَإِن تَتَوَلَّوْا يَسْتَبْدِلْ قَوْمًا غَيْرَكُمْ ثُمَّ لَا يَكُونُوا أَمْثَالَكُم ﴾

اللهم استعملنا ولا تستبدلنا

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Quiz on last lecture

Drug Clearance (CL)

(CL) Unit: volume/time

- **It is the volume of (blood or plasma) that is completely cleared of drug per unit time.**
- **It is a measure of the ability of the body to eliminate (and distribute) the drug.**
- **Clearance of a drug is the factor that predicts the rate of elimination in relation to the drug concentration:**

  CL = rate of elimination/Cp

- Note that (CL) differs from elimination rate.
- The **elimination rate** is measured in terms of amount per unit of time,
- whereas **clearance** is measured in terms of volume per unit of time.

Drug Clearance (CL)

- Assume that the unit for elimination rate is mg/hour, while concentration is measured in mg per liter. When applied to the equation (**CL = rate of elimination/Cp**), this yields the unit for clearance, which is **liters/hour.**

❖ **Assume that the rate of elimination of a drug is 10 mg/hour, and the plasma concentration is 1 mg/L. What is drug clearance?**

CL = [10 mg/hour] / [1 mg/L] = 10 L/hour

Extra slide (elimination of drugs)

- Occur in various ways: exerted through urine, bile, saliva, and even in exhaled breath.
- A drug may be directly excreted or metabolized first and then eliminated.
- When applying the **Total Clearance Equation**, we sum all elimination pathways relevant to the drug. Often, more than one of these methods contributes to overall clearance.

Drug Clearance (CL)

- **There may be more than one method of elimination, and thus the rate of elimination will be the sum of all these methods.**

The most important clearance paths are hepatic and renal. See details next.

- **Renal clearance (CL_R) = (Cu*V)/Cp**

  Where:

  - **Cu is concentration of drug in urine.**
  - **V is urine flow rate** (Volume/time).
  - **Cp is the plasma concentration of the drug.**

This procedure (renal clearance calculation) is easy to apply and can be observed during your clinical rotations in the future. **See next slide.**

Renal clearance (CL_R) procedure. Extra slide.

- To measure renal clearance, ask the patient to empty their bladder and then collect urine over a specified period (usually 24 hours). If needed, a catheter can be used.
- After 24 hours, measure the total urine volume, for example, 2 liters. To calculate **urine flow rate (V)**, divide the total volume (2 liters) by the collection time (24 hours), yielding a urine flow rate.
- Next, collect a urine sample and measure the **drug concentration in urine (Cu).**
- For **plasma concentration (Cp)**, take a blood sample at the **midpoint** of the collection period (12 hours after the start of the 24-hour collection period). This is because the Cp is continuously changing; we need a Cp value that is representative of the whole interval.

Drug Clearance (CL)

Direct equation

- **Hepatic clearance (CL_H) =**

[(blood flow. C_i) - (blood flow. C_o)]/ C_i

CL_H = blood flow * (C_i- C_o)/C_i

CL_H = Q*ER

$$ER = (C_i - C_o)/C_i$$

- C_i is drug concentration in blood going to the liver.
- C_o is drug concentration in blood leaving the liver
- Q is blood flow.
- ER is the extraction ratio of the drug.

The liver receives blood from the
1. Hepatic artery (from the systematic circulation).
2. Portal vein (from the intestines).

Blood leaves the liver through the hepatic vein.

We can use this to answer Qs theoretically.

Drug Clearance (CL)

- There are other indirect equations that can be used to calculate hepatic clearance.
- The previous equation for calculating hepatic clearance through catheterization of the hepatic artery, portal artery, and portal vein is considered unethical and illegal (it is only theoretical).
- This invasive procedure carries significant risks and should not be performed. If attempted, it would typically require abdominal surgery to access these vessels. Informed consent from the patient is essential, and such a procedure should only be considered in exceptional cases under strict ethical guidelines.

it's unlikely to be a question on exams. Still, it's good to know as a doctor.

First-Order Drug Elimination

A drug can undergo first-order, zero-order, or flow-dependent elimination.

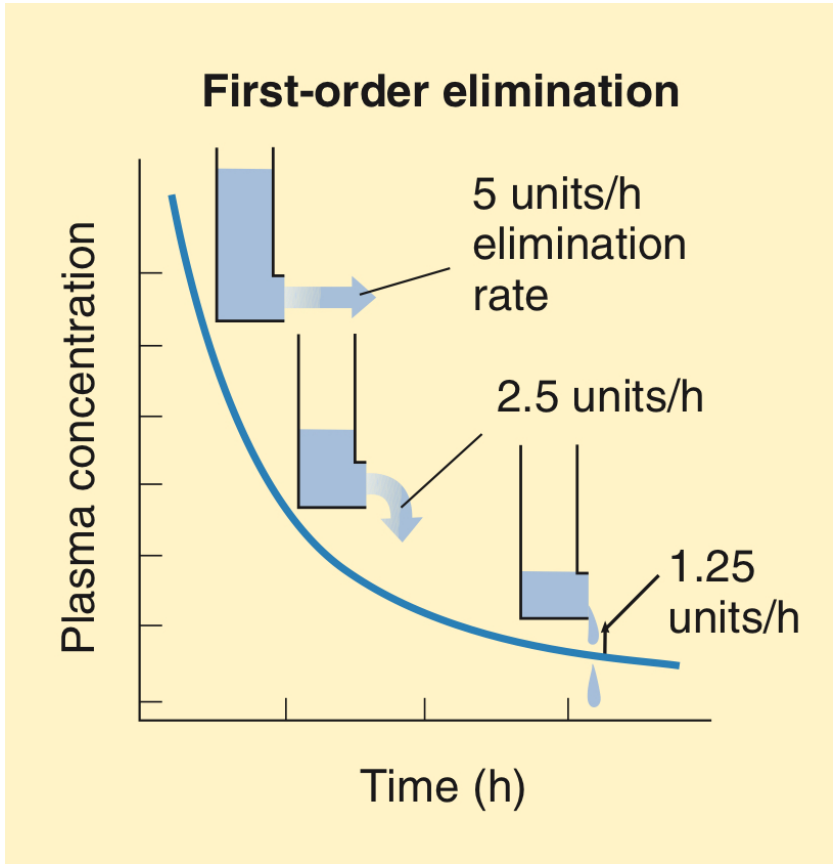
- It occurs when the rate of drug elimination is directly proportional to the amount of drug in the body.
- Occurs with many drugs at therapeutic concentrations.
- A constant fraction of the drug is eliminated per unit time.
- The elimination rate constant is designated as **"k"**, and its units are reciprocal time (1/time) **meaning fraction per unit time.**

- **The rate of elimination is proportional to the amount of drug in the body, with a constant fraction being eliminated rather than a constant amount.**

zero-order
(discussed later)

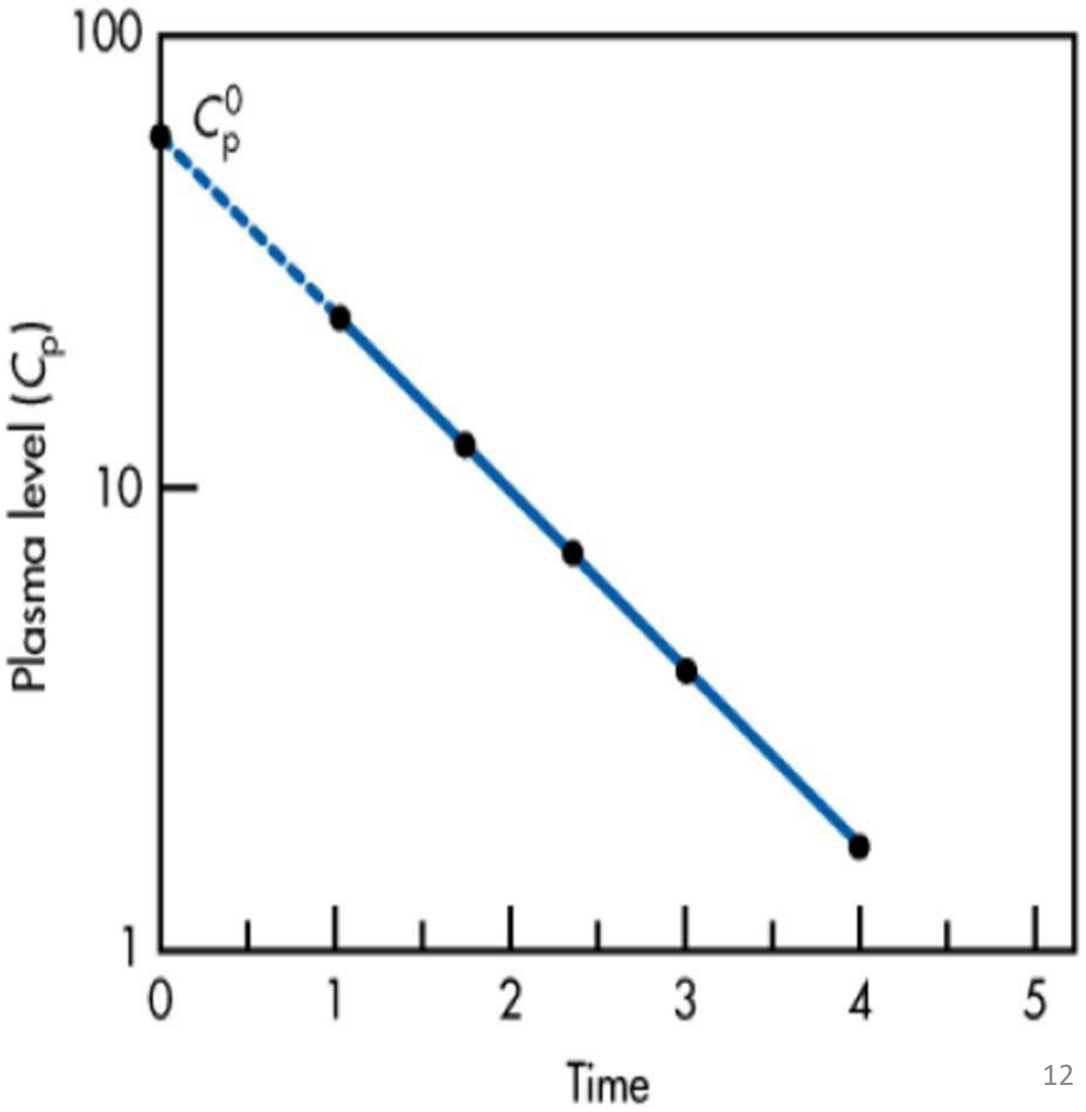
First-Order Drug Elimination **Extra slide**

- First-order elimination means the rate of drug elimination is **proportional** to its concentration, so as the concentration increases, more drug is eliminated per unit time.
- Assuming the elimination rate **constant** (K) is 10% per hour, and we start with 100 mg of a drug, after one hour, 10 mg will be eliminated, leaving 90 mg. After another hour, 10% of 90 mg (or 9 mg) will be eliminated, leaving 81 mg, and so on.
- This elimination (first-order) is good in cases of overdoes or toxicity since the drug will be faster eliminated if its concentration is high.



1. **Plasma Concentration vs. Time Plot**:
· **X-axis**: Time (linear scale)
· **Y-axis**: Plasma concentration (logarithmic scale)
· This suggests that the drug is undergoing first-order elimination, where its concentration decreases exponentially over time.
2. **Key Points**:
· **Initial Concentration** (Cp^0): The concentration of the drug at time zero (immediately after administration). Used in calculating volume of distribution.
· **Downward Slope**: Represents the exponential decrease in drug concentration over time.
· **Confirming First-Order Kinetics**: A straight line in this "semi-logarithmic plot" indicates first-order elimination. Multiple data points (4-5) are used to ensure accuracy and confirm this relationship.
· **Half-Life Calculation**: By measuring the time it takes for the drug concentration to halve, you can calculate the drug's half-life, which is crucial for dosing decisions.

Cp^0 is theoretically obtained by extrapolating the line
It is the concentration used in calculating V_d

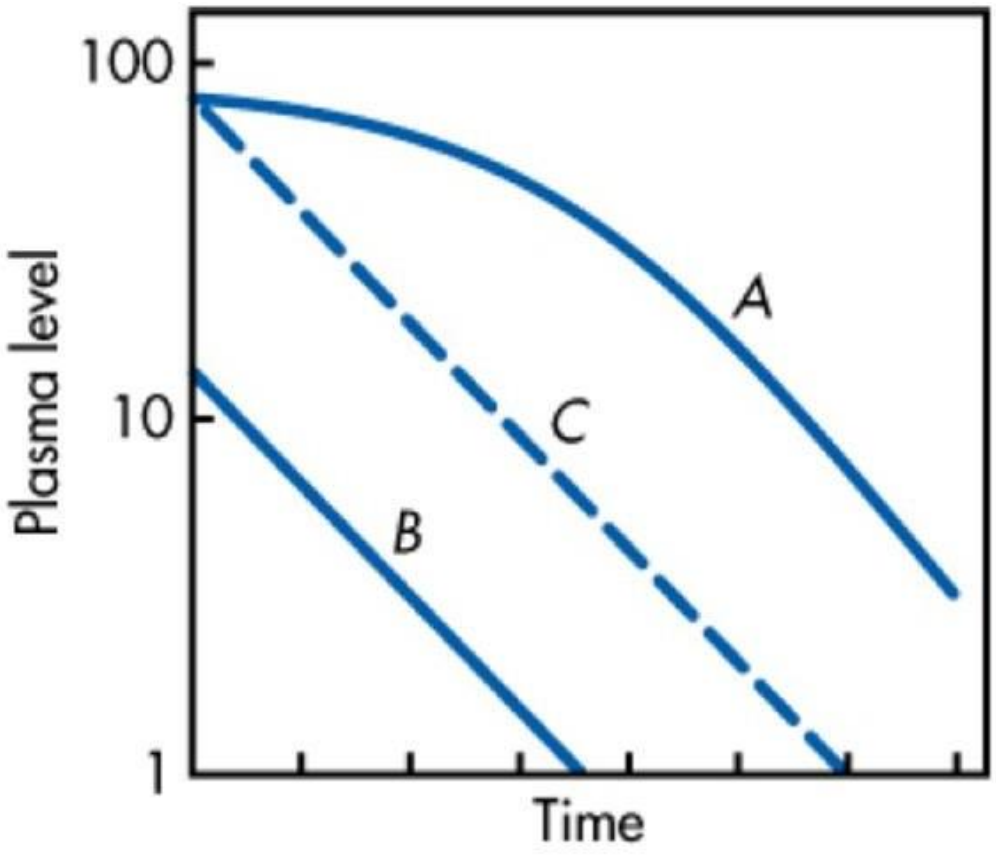


Zero-Order Drug Elimination

- **Also called Saturable elimination.**
- **Occurs with few drugs (aspirin, phenytoin, ethanol, ..).**
- **Elimination rate is NOT proportional to the amount of drug in the body, but a constant amount is removed per unit time, because of saturation of the elimination process.**

- It depends on the enzyme that metabolizes a drug if it's saturable **at therapeutic range** or not, and it could be catastrophic to the body if the administration isn't calculated properly (overdose).

Semi-logarithmic plot



- “A” represents a drug elimination figure, it starts with a constant amount of removal at high concentrations with a non-linear approach, and after a while, it adopts a linear relation (as the drug concentration is below saturation level).
- “C” is a hypothetical figure showing how the mechanism would be if it were first-order elimination.
- “B” displays the linear part of Figure “A”.

Source: Shargel L, Wu-Pong S, Yu ABC: *Applied Biopharmaceutics & Pharmacokinetics, 6th Edition*: www.accesspharmacy.com

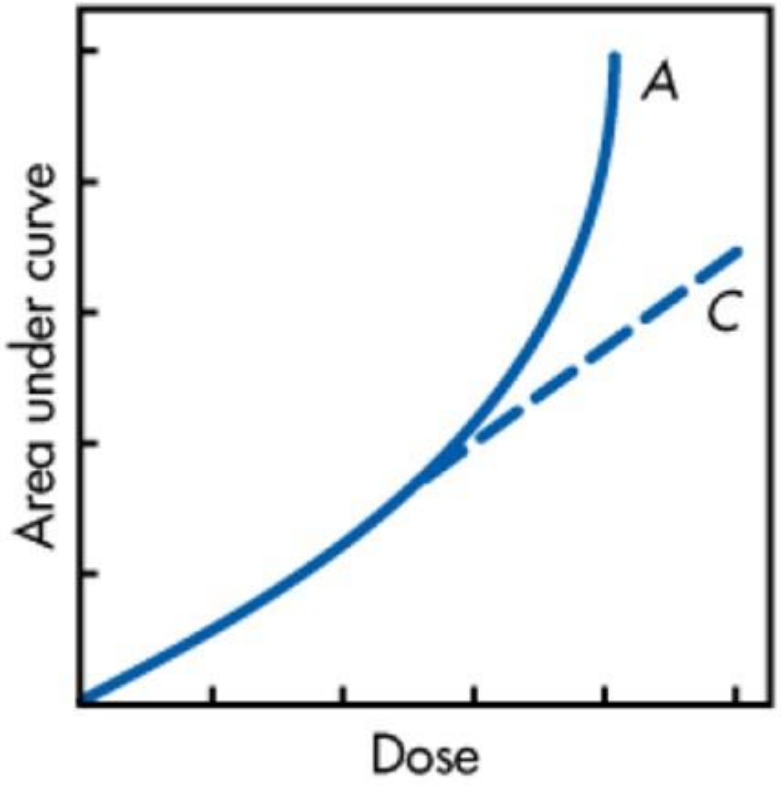
Zero-Order Drug Elimination

- **Rate of elimination = (V_{max}* C) / (K_m + C)**

Where:

- **V_{max} is the maximal elimination capacity**
- **K_m is the drug concentration at which rate of elimination = ½ V_{max}.**

- At zero-order elimination, the rate of elimination is constant and called K_O (K zero) with a dimension of (mass/time); it's also challenging to use this kind of drug if it's needed to adjust the dose as elimination isn't proportional to the Cp.
- For first-order kinetics, the case it a lot easier. For example, if we want to double Cp, we can simply double the dose.



Source: Shargel L, Wu-Pong S, Yu ABC: *Applied Biopharmaceutics & Pharmacokinetics, 6th Edition*: www.accesspharmacy.com

- Figure "A" represents a zero-order drug elimination, it's obvious how dangerous it is to increase the dose haphazardly where Area under curve (or Cp) increases exponentially at some point in time.
- It is good that only some drugs undergo zero-order kinetics at therapeutic conc.

Curve C represent first-order kinetics

Flow-Dependent Drug Elimination

- **Some drugs are cleared very rapidly by the organ of elimination (liver), so that at clinical concentrations of the drug, most of the drug perfusing the liver is eliminated on first pass through it.**
- **Rate of elimination is determined by the rate of hepatic blood flow.** (It is proportional to the rate of hepatic blood flow.)
- **Drugs that have this property are called "high extraction ratio" drugs.**

(Or extensive first-pass effect, as this type of drug is cleared rapidly by the liver at clinical concentrations as it enters for its first time.)

- **Include <u>morphine, lidocaine, propranolol, verapamil,</u> and others.**

Half-Life (t½) of Elimination

- **It is the time required for the amount of drug in the body or the plasma concentration of the drug (assuming first-order elimination) to drop by 50%.**
- **In this case it is constant, and not related to dose.**
- **After ~ 4 half-lives, most of the drug will be eliminated from the body.**
- **It is related to first-order elimination rate constant such that:**

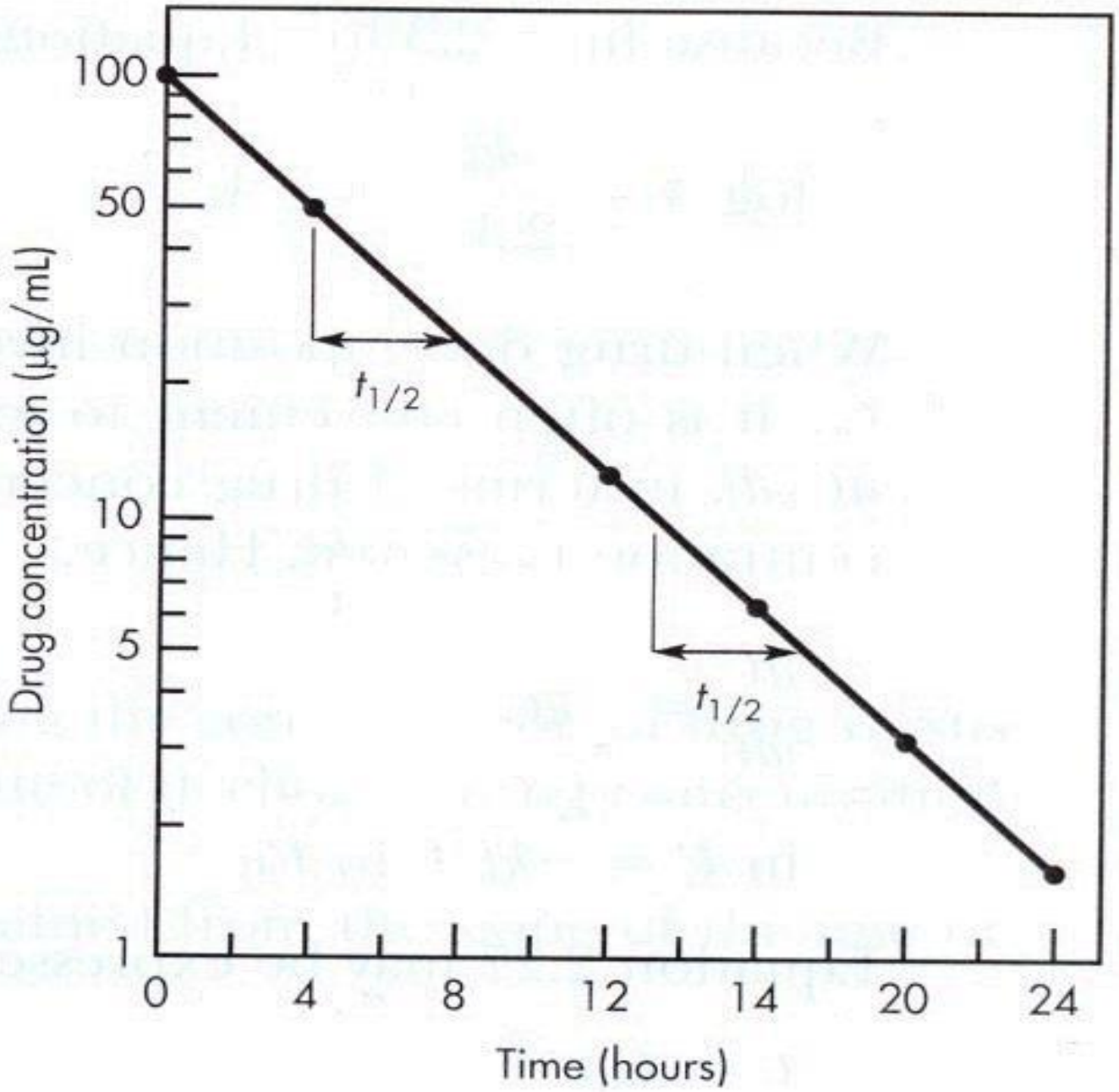
$$k \times t_{1/2} = 0.693$$

$$\ln(2) \approx 0.693$$

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

- After the first four half-lives, the remaining concentration is considered insignificant (6.25%).

All equations should be memorized.



To calculate $t_{1/2}$ by using a first-order figure, observe the time needed to clear half of the concentration at any two points, for example, 100 and 50 or 10 and 5 (as y-axis).

Here half-life is 4 hours.

Half-Life (t½) of Elimination

- **The half-life is related to volume of distribution and clearance for drugs that follow first-order kinetics by the following equation:**

CL = k * Vd

t½ = 0.693 * Vd/CL

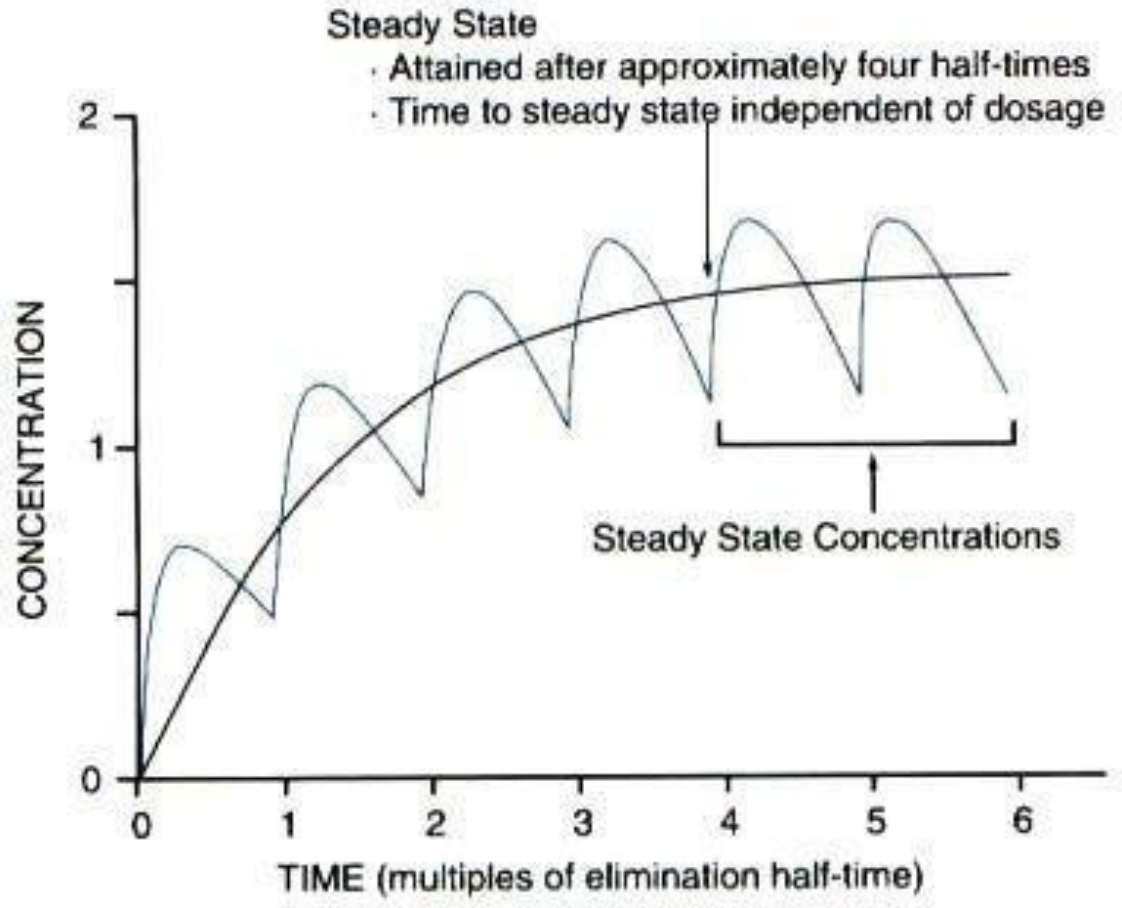
- Clearance is dependent on both k and Vd, as it's concerned about the volume of blood "clear" from a drug whether it distributes to tissues or gets eliminated out of the body.

Half-Life (t½) of Elimination

- **It is related to dose and plasma concentration for drugs undergoing zero-order kinetics, and is NOT constant.**
- **The higher the concentration, the longer the half-life of elimination and vice versa.**

Steady-State

- **Steady-state is a condition achieved following repeated drug administration as occurs in clinical practice.**
- **It occurs when the rate of drug administration (dosing rate) is equal to the rate of drug elimination.**
- **At steady-state, a constant peak, trough, and average drug concentrations are achieved.**



- This figure shows the Cp of a drug related to time (displayed as multiples of $t_{1/2}$), the drug is firstly administered with a concentration equivalent to 1.

- After one $t_{1/2}$ it becomes 0.5 → an additional administration is done making the total Cp = 1.5 and of the 1.5, only 0.75 remains after another $t_{1/2}$, so when the dose is repeated, Cp turn into 1.75

- This is repeated until the concentration is considered constant (after 4 half-lives or more) as long as more doses are introduced periodically.

- Note that the fluctuated figure *-with peaks and troughs-* shows an oral administration route, while the other one symbolizes an IV route (or the average concentrations) where the graph is smooth.

Steady-State

- **Steady-state is achieved after approximately 4 half-lives of repeated drug administration.**
- **50% of SS is achieved after one half-life of administration.**
- **Our aim during drug therapy is to attain a steady-state drug concentration (Css) within the therapeutic range, but NOT subtherapeutic or toxic.**

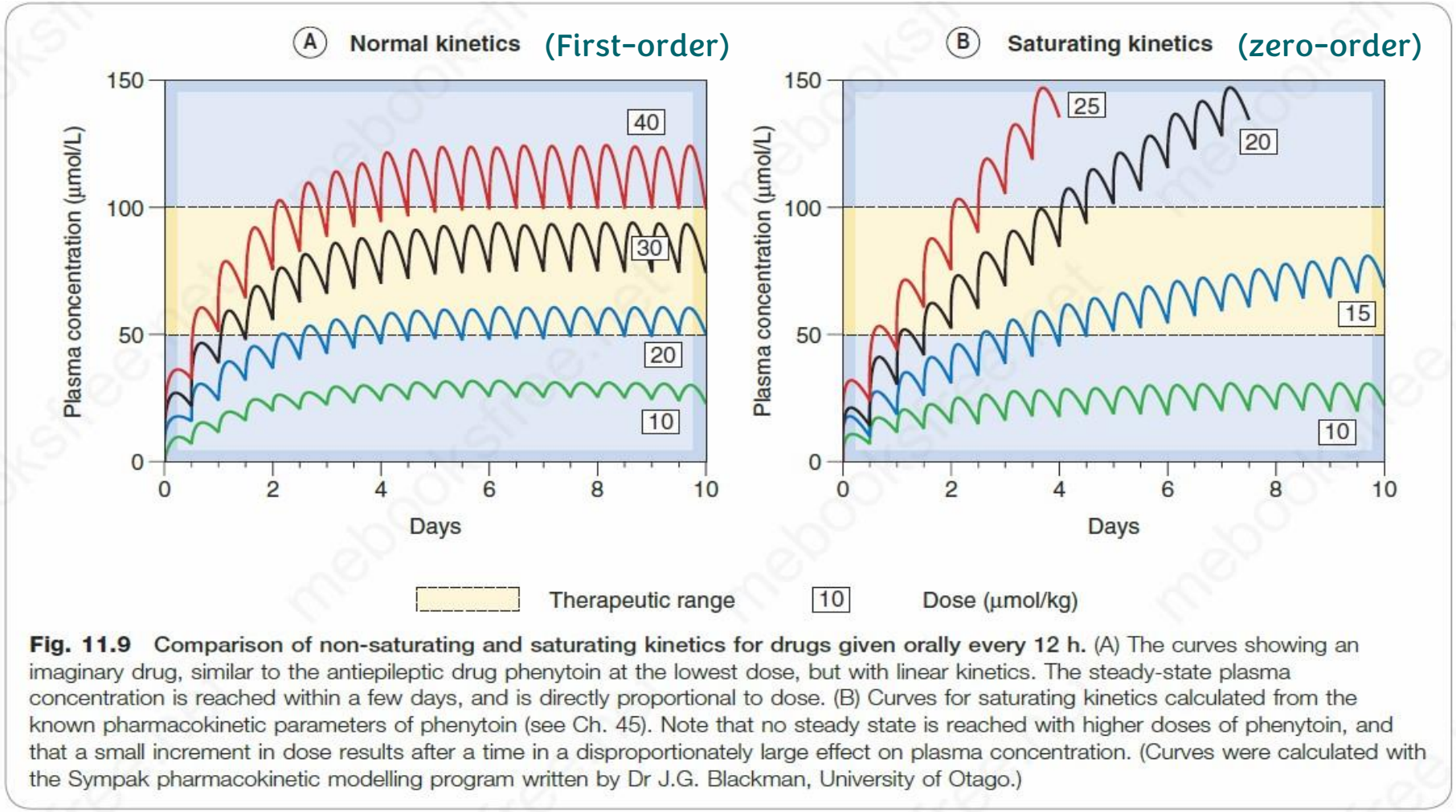


Fig. 11.9 Comparison of non-saturating and saturating kinetics for drugs given orally every 12 h. (A) The curves showing an imaginary drug, similar to the antiepileptic drug phenytoin at the lowest dose, but with linear kinetics. The steady-state plasma concentration is reached within a few days, and is directly proportional to dose. (B) Curves for saturating kinetics calculated from the known pharmacokinetic parameters of phenytoin (see Ch. 45). Note that no steady state is reached with higher doses of phenytoin, and that a small increment in dose results after a time in a disproportionately large effect on plasma concentration. (Curves were calculated with the Sympak pharmacokinetic modelling program written by Dr J.G. Blackman, University of Otago.)

- Following the first order, a Css is going to be achieved no matter what the repeated dose is, and they are proportional to one another (a dose equal to 10 mg would give a given Css, and after doubling that repeated dose the Css will be doubled also, which is **a linear relationship.**
- Zero-order on the other hand doesn't hold a proportional relationship, which makes adjusting a dose proportionately to Css non-practical.

Loading Dose (LD)

- **When the half-life is too long, steady-state will take a long time to be achieved.**
- **Therefore, we may need to give a loading dose to achieve drug concentration within the therapeutic range sooner (target concentration).**

$$LD = V_D * Css_{desired}$$

LD could be given orally or intravenously, also sometimes it is given gradually (to avoid toxicity).

Maintenance Dose (MD)

- **To attain and maintain a desired Css of a drug, we need to adjust the dose so that, the rate of drug administration is equal to the rate of drug elimination.**
- **Elimination is a function of clearance.**

$$\mathbf{MD = CL * Css_{desired}}$$

$Css_{desired}$ is also called the target concentration.

Pharmacokinetics Equations Summary

Drug Clearance (CL) Formula:

$CL = \text{rate of elimination} / Cp$

Renal Clearance (CLR) Formula:

$CL_R = (Cu * V) / Cp$

Hepatic Clearance (CLH) Formula:

$CL_H = (Q * (Ci - Co)) / Ci) = Q * ER$

First-Order Elimination Rate:

$\text{Rate of elimination} = k * [\text{Drug}]$

Half-Life ($t_{1/2}$) - First-Order Kinetics:

$t_{1/2} = 0.693 / k$

Clearance (CL) Relationship in First-Order:

$CL = k * Vd$

Half-Life ($t_{1/2}$) - First-Order with Volume of Distribution:

$t_{1/2} = 0.693 * (Vd / CL)$

Zero-Order Elimination Rate:

$\text{Rate of elimination} = V_{max} * C / (K_m + C)$

Loading Dose (LD):

$LD = Vd * Css_{desired}$

Maintenance Dose (MD):

$MD = CL * Css_{desired}$

Summary

1. Drug Clearance (CL)

The fundamental measure of drug elimination power.

· Defines the volume of plasma cleared of the drug per unit time, directly predicting elimination rate.

· Key for calculating dosing and understanding drug removal via **different pathways.**

2. **Elimination Kinetics: Precision in Drug Safety**

· **First-Order**: A dynamic, concentration-proportional process where a **constant fraction** is eliminated per time – common in many drugs at therapeutic levels.

· **Zero-Order**: A **fixed amount** is eliminated regardless of concentration due to enzyme saturation (e.g., aspirin, ethanol). Missteps here can lead to toxic buildup.

· **Flow-Dependent**: For high extraction drugs, **organ blood flow** determines elimination, key in designing high-efficacy, rapid-clearing drugs.

Summary

3. **Half-Life (t½): The Heart of Dosing**
· Governs dosing intervals by indicating how long it takes for the drug's plasma concentration to half.
· Essential in planning steady therapeutic levels; requires calculating differently based on **first- or zero-order** kinetics.

4. **Steady-State Concentration (Css): The Therapeutic Target**
· Achieved after approximately four half-lives of repeated dosing, **where dosing rate matches elimination rate** – the goal for effective and safe drug therapy.
· Distinct profiles: **Linear and predictable in first-order**; complex and non-linear in zero-order, where dosage increases can lead to dramatic concentration rises.

5. **Strategic Dosing**
· **Loading Dose (LD)**: Critical for achieving therapeutic concentration swiftly when immediate drug action is needed and the half-life is relatively long.
· **Maintenance Dose (MD)**: Balances elimination to **sustain steady-state** within the therapeutic range, ensuring efficacy without toxicity.

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:

بقدر الكد تكتسب المـــعالي ومن طلب العلا سهر اللـيالي
ومن طلب العلا من غير كد أضاع العمر في طلب المحالِ

Extra References for the Reader to Use:

1. Lippincott illustrated reviews
   Chapter 1

2. Katzung basic & clinical pharmacology
   Chapter 3