بسم الله الرحمٰن الرحيم

(وَفَوْقَ كُلِّ ذِي عِلْمٍ عَلِيمٌ)

Pharmacology | Lecture #11

Pharmacokinetics Pt.5

Written by : Leen Alzoubi
Reem Alfaqeh

Reviewed by : Maram Darweesh

Half-life is constant only in **first-order drugs** because the rate of elimination is proportional to the amount of the drug in the body

Half-Life (t½) of Elimination

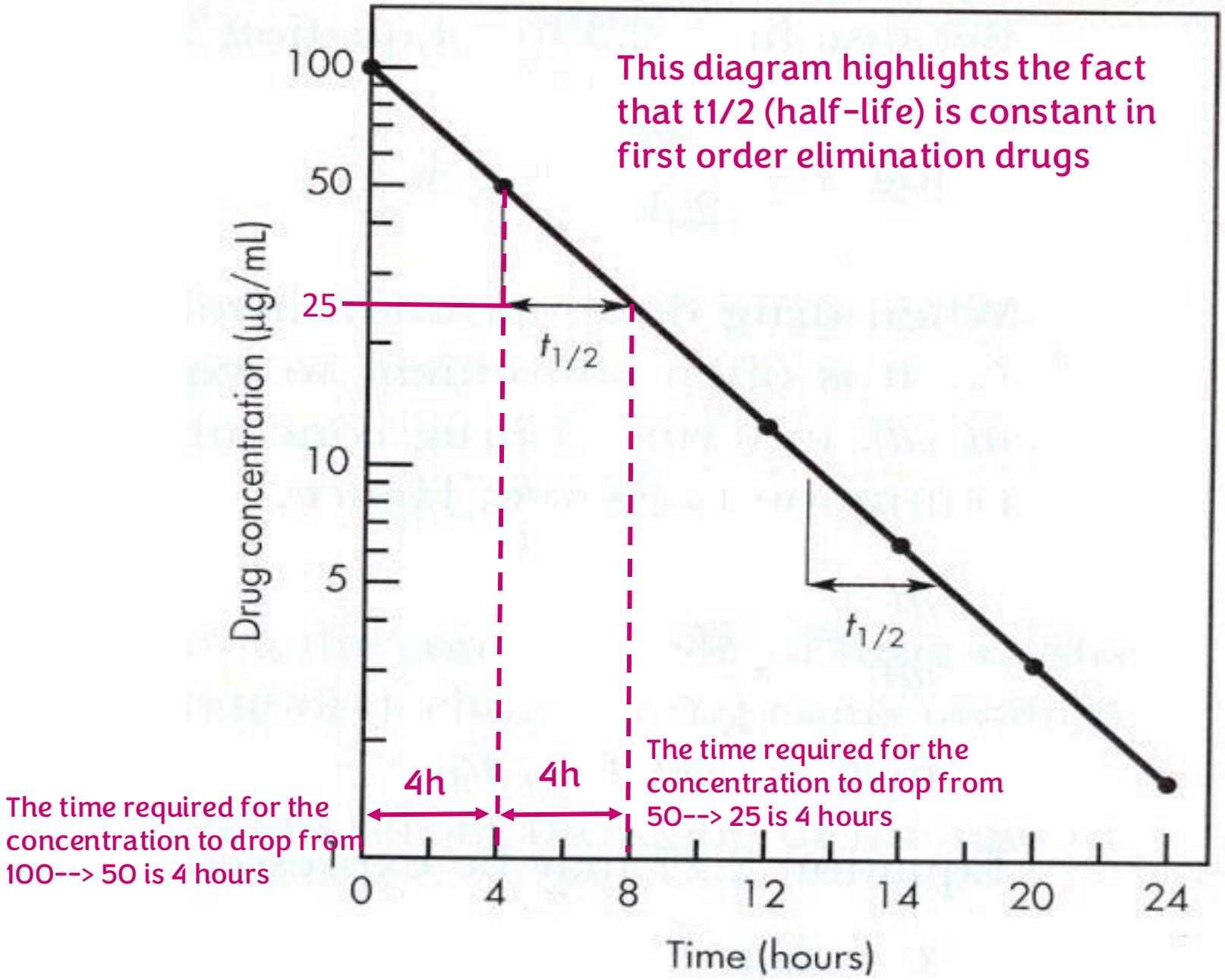
- It is the time required for the amount of drug in the body or the plasma concentration of the drug (assuming first-order elimination) to drop by 50%.
- In this case it is constant, and not related to dose.
- After ~ 4 half-lives, most of the drug will be eliminated from the body.
- It is related to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

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

This equation is important! (memorize it)

Half-lives	% of drug removed	% of remaining drug
1	50	50
2	75 50+25	25
3	87.5 50+25+12.5	12.5
4	93.75 50+25+12.5+6.25	6.25

For a single dose: After **4 half-lives** almost 94% of the drug will be removed from the body


This diagram highlights the fact that t1/2 (half-life) is constant in first order elimination drugs
100
50
25
10
5
Drug concentration (µg/mL)
$t_{1/2}$
$t_{1/2}$
4h
4h
The time required for the concentration to drop from 100--> 50 is 4 hours
The time required for the concentration to drop from 50--> 25 is 4 hours
0
4
8
12
14
20
24
Time (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:**

Total body clearance ← $CL = k.Vd$

$t½ = 0.693\ Vd/CL$

Important equations!

- CL(clearance) is the disappearance of drug from the plasma/ blood thus it includes both the elimination of the drug (K) and the distribution of the drug (Vd) as seen in the equation
- T1/2 is inversely proportional to K

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.

Example,
The body eliminates 10mg/h (zero-order elimination) what is the half-life of the drug? It depends on the dose
If we have 100mg dose, then t1/2= 5 hours
If we have 200mg dose, then t1/2= 10 hours
If we have 1000mg dose, then t1/2= 50 hours

Steady-State

- **Steady-state is a condition achieved following repeated drug administration as occurs in clinical practice.** We are not talking about a single dose, most medications require repeated dosing (daily, weekly, monthly, or lifelong depending on the condition).
- **It occurs when the rate of drug administration (dosing rate) is equal to the rate of drug elimination.**
- **At steady-state, a constant peak (قمة), trough (قاع), and average drug concentrations are achieved.**

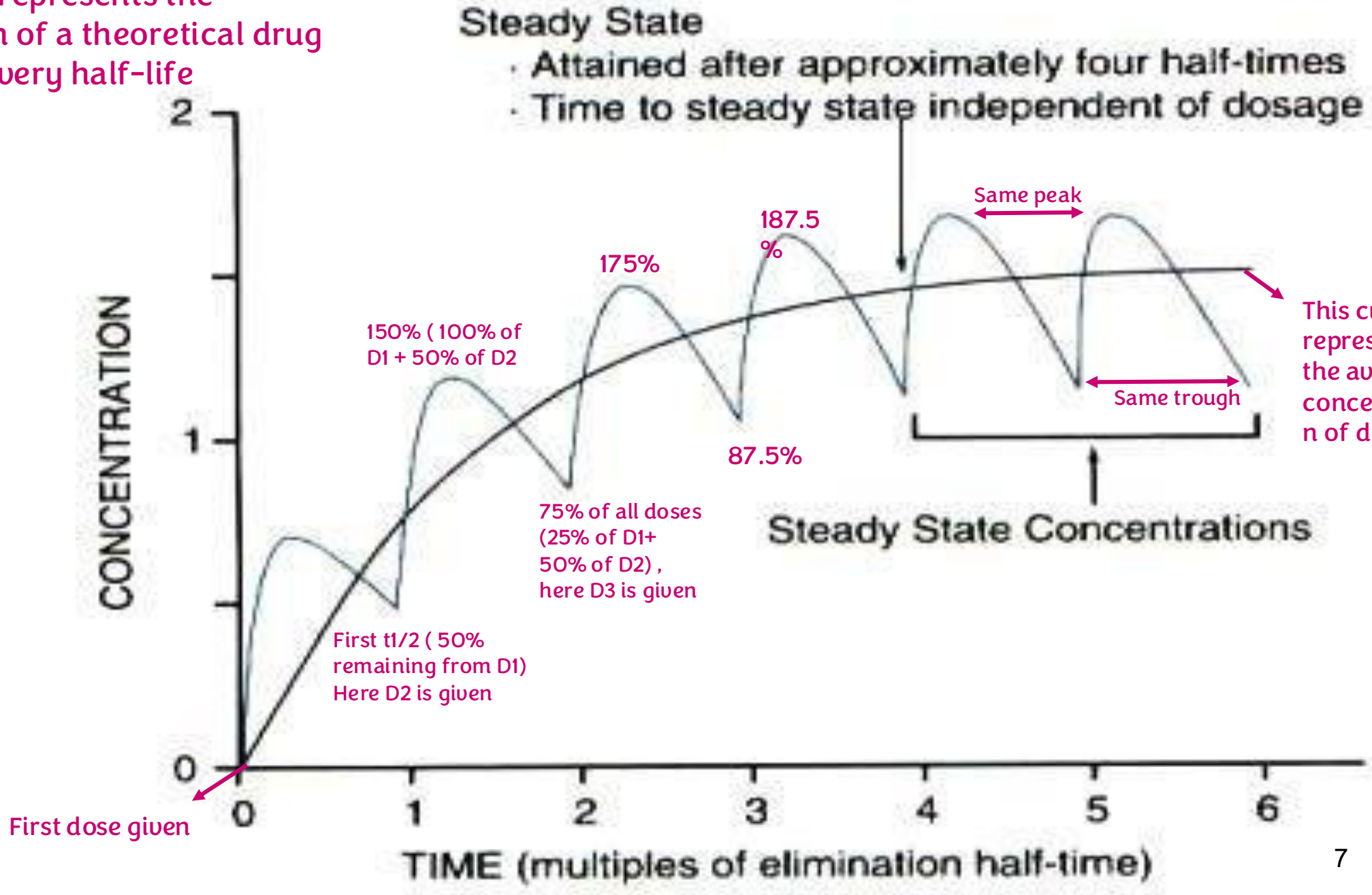
- **Oral dosing** produces *peaks* and *troughs* because the drug is given intermittently (not continuous) → concentration fluctuates.
- **IV infusion (not injection)** provides a very small continuous amount of the drug per minute, so the concentration rises smoothly with minimal fluctuation, and steady state is reached in the same way (after 4 half-lives).

This diagram represents the concentration of a theoretical drug given orally every half-life

D1 : Dose 1

D2 : Dose 2

D3: Dose 3



Average Concentration

- The average concentration at steady state forms a plateau on the graph (a line parallel to the x-axis).
- With IV infusion, the concentration follows a similar smooth rise toward this average line because the input is continuous.
- The average steady-state concentration is NOT equal to *(peak + trough) ÷ 2*

Steady State Definition

- Steady state occurs when the drug concentration becomes constant after repeated dosing.
- At steady state, each dose produces the same peak (maximum concentration).
- Each dose also produces the same trough (minimum concentration before the next dose).

Time to Reach Steady State

- It takes about four half-lives to reach steady state, provided the drug is given at consistent, regular intervals.

Conditions Required to Achieve Steady State

To reach and maintain steady state, drug administration must be:

- Repeated (not a single dose)
- Regular (given on a fixed schedule)
- Continuous or consistent (no large gaps or irregular spacing of doses)

Best Method to Maintain Steady State

- IV infusion provides the most stable and precise steady-state concentration.
- However, the patient must remain in the hospital for the entire treatment duration.

Clinical Use of Infusion

- IV infusion is used only in emergencies or acute, critical cases.
- It is not practical for routine or long-term drug administration

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.**

To treat a disease, we need a constant concentration of the drug in the body, because the action of the drug is related to the plasma concentration of the drug, so we need a specific concentration that gives the desired effect

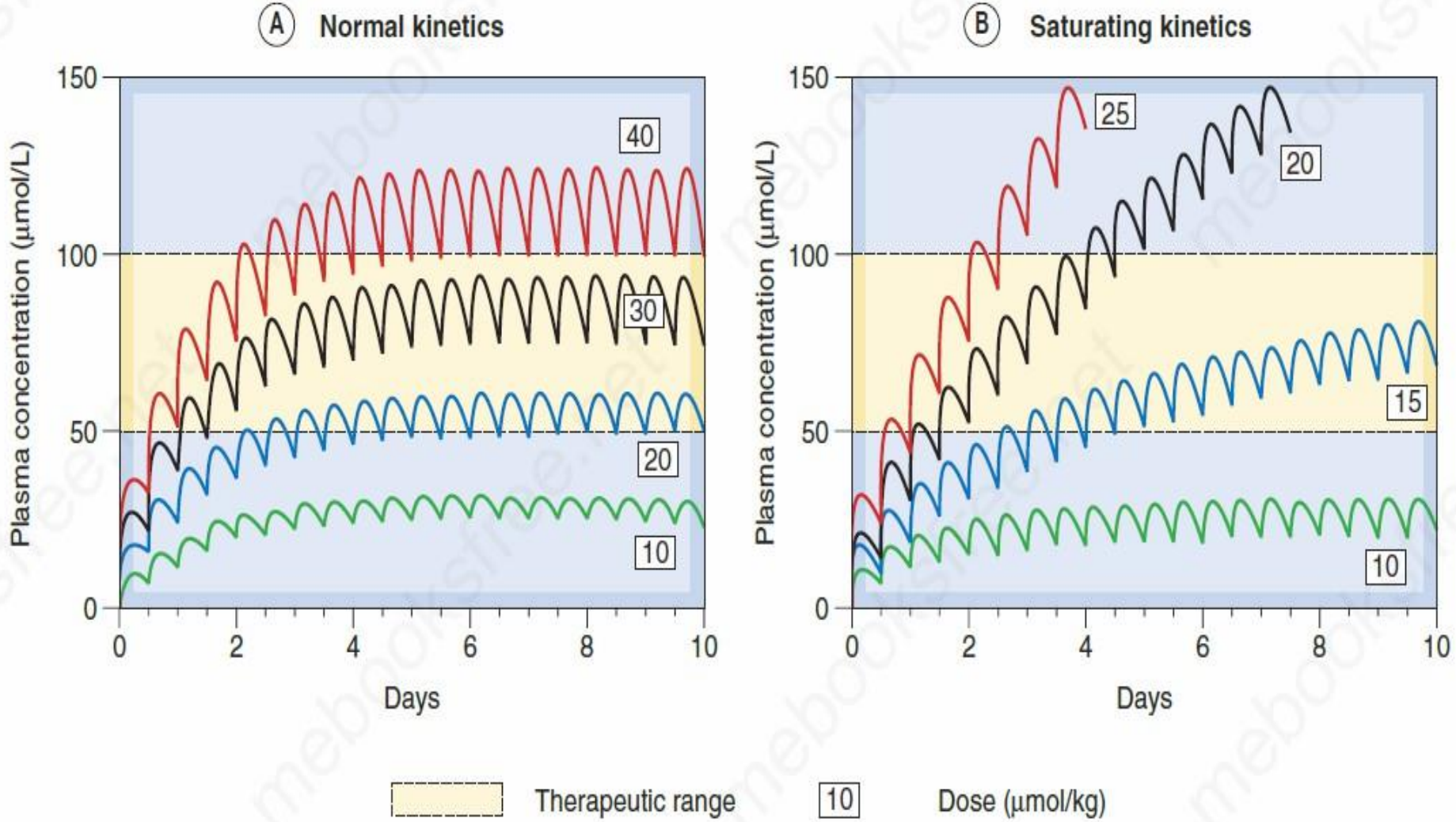
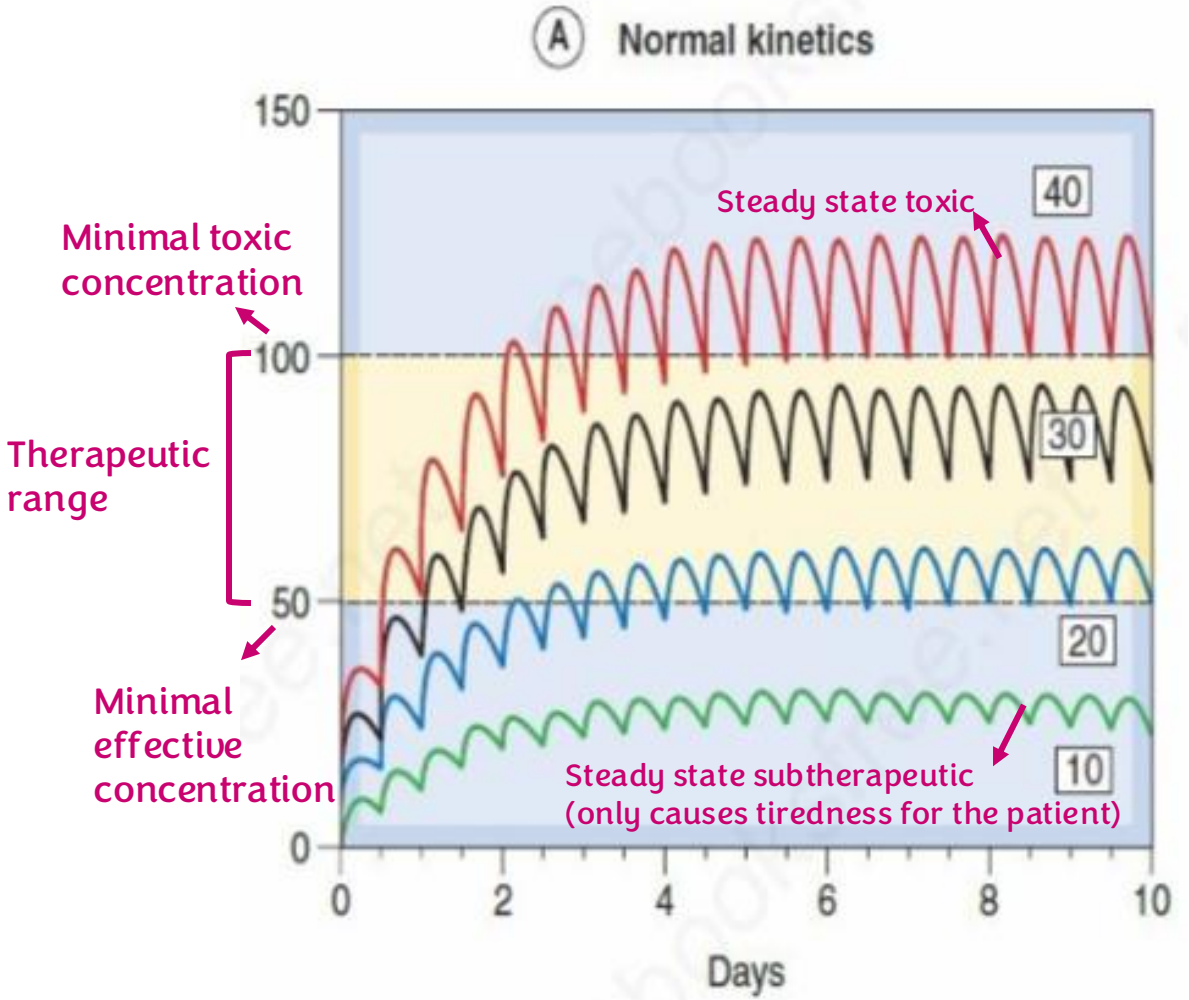


Fig. 11.9 Comparison of non-saturating and saturating kinetics for drugs given orally every 12 h. (A) The curves showing an imaginary drug, similar to the antiepileptic drug phenytoin at the lowest dose, but with linear kinetics. The steady-state plasma concentration is reached within a few days, and 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.)

First order drugs



General Concepts

- In first-order kinetics, drug concentration in the plasma is proportional to the dose.
- Increasing the dose (e.g., doubling or tripling it) will produce a proportional increase in the steady-state concentration.

Therapeutic Range

- The yellow shaded area shows the therapeutic range.
- To achieve the desired effect, the steady-state concentration must remain within this range – not below it (subtherapeutic) and not above it (toxic).

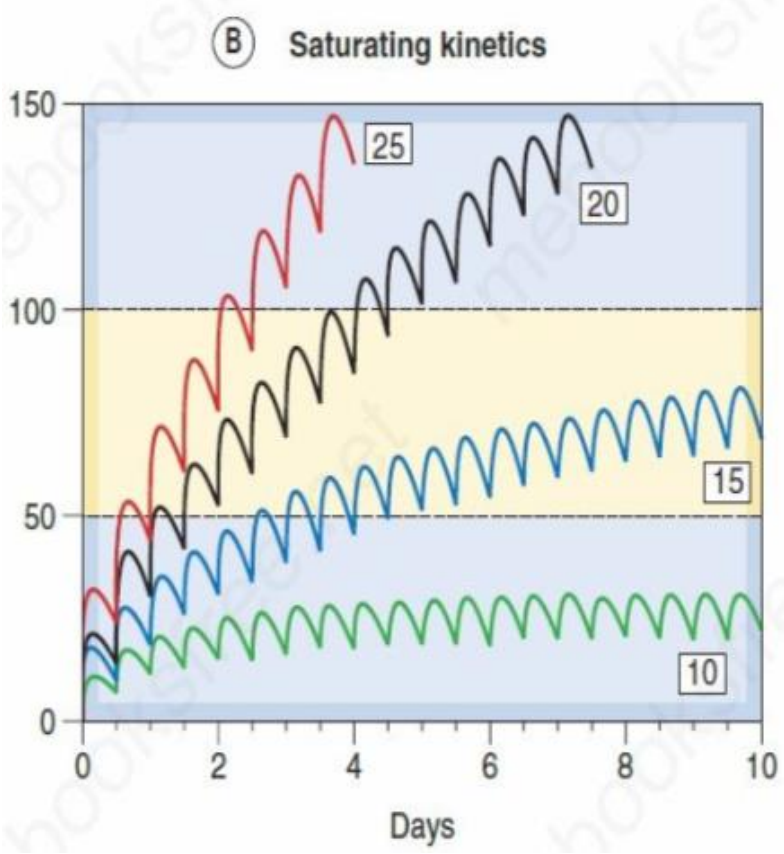
Dose Examples

- High dose (red line): Steady state enters the toxic range.
- Moderate dose (black line): Steady state lies within the therapeutic range – optimal.
- Low dose (blue/green lines): Steady state falls below the therapeutic range, causing only mild effects or no effect (subtherapeutic).

Clinical Meaning

- We need steady state to fall within the therapeutic window to ensure both safety and effectiveness.
- If the concentration goes above the upper limit → toxicity.
- If it stays below the minimal effective concentration → no therapeutic benefit.

Zero order drugs



General Concept

- In zero-order kinetics, the elimination process becomes saturated.
- The body cannot eliminate the drug faster, no matter how much the concentration increases.

Effect of Increasing the Dose

- You cannot double the dose and expect a proportional increase — the system goes out of control.
- Even a small increase in dose can cause a large, unpredictable rise in plasma concentration.

No True Steady State

- Because elimination is saturated, the drug concentration keeps rising with each dose.
- The system cannot reach steady state, unlike in first-order kinetics.
- This continuing accumulation can lead to toxicity, even if the dose seems reasonable.

Dose Examples

- **High dose (red line):**
  Concentration rises steeply and enters the toxic range rapidly.
- **Moderate dose (black line):**
  Still shows continuous accumulation, no steady state.
- **Lower dose (blue line):**
  Less accumulation but still not stable — concentration keeps increasing.
- **Very low dose (green line):**
  May produce a subtherapeutic steady level, but this is only because the dose is too small to cause saturation.

Clinical Meaning

- Drugs with zero-order elimination are dangerous because small dose changes can cause massive increases in drug levels.
- They require very careful monitoring.

Loading Dose (LD)

If the drug has a half-life of 24 hours, it means it needs about 5 -4half-lives (4 ≈days) to reach the steady state.
We cannot leave the patient untreated for four days, so we give a loading dose to reach the therapeutic level immediately.

- **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).**

$$LD = V_D \cdot Css_{desired}$$

Steady state concentration desired

Therapeutic

Loading Dose (LD)

Loading dose:

It is a single large dose given once at the beginning of therapy to rapidly reach the therapeutic concentration of the drug in the blood.

Relation to half-life (t½):

If a drug has a long half-life, it would normally take a long time to reach the steady therapeutic level with regular doses.

Therefore, a loading dose is given to reach that level quickly, instead of waiting for several half-lives.

It is given in emergency cases.

We give it to fill the volume of distribution (Vd)

After that, we start giving maintenance doses.

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 clearnce.**

$$MD = CL.\ Css_{desired}$$

CL: $\frac{\text{Volume}}{\text{Time}}$ $Css_{desired}$: $\frac{\text{Mass}}{\text{Volume}}$

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

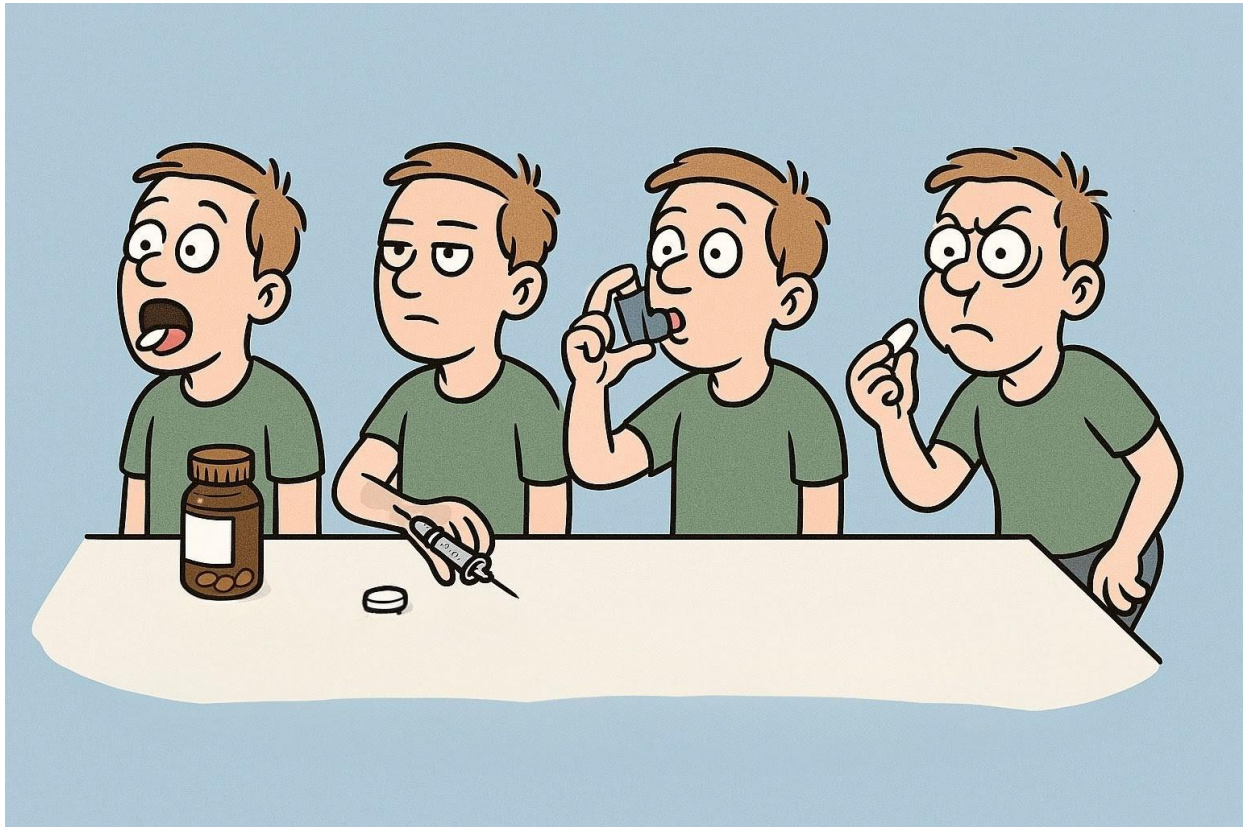
Maintenance dose

<It replaces what the body loses every day.
Because we always have a daily loss, the maintenance dose is given to compensate for that loss.

What goes out from the plasma is the clearance (CL).
That's why the formula is:
Maintenance dose rate = CL × Css

The unit is mass/time, because it's a rate –we give it every 6 or 12 hours, for example.

Routes of Drug Administration



Yacoub Irshaid MD, PhD, ABCP

Department of Pharmacology

Routes of Drug Administration

A. **Enteral** — Giving a drug through the gastrointestinal tract (GIT)
B. **Parenteral**
C. **Others**

Enteral Routes

1. **Oral route (PO):** PO = per os

Oral drugs should be swallowed with tepid (lukewarm) water, not cold water, juice, tea, or herbal infusions

- The drug should be swallowed.
- Most commonly used route.
- Safest, most convenient, and most economical

Oral administration is considered the safest because these complications do not occur.
With injections, whether intravenous (IV) or intramuscular (IM), bacteria can enter from the needle, or the needle can hit and damage a nerve

- Duodenum is the major site of absorption, but stomach, jejunum and ileum may be involved.

Enteral Routes

Most absorption occurs in the duodenum because:

It has folds that increase the surface area.

It has villi and microvilli (small projections) that further increase the surface area.

The large intestine is not suitable for absorption of drugs.
Its main function is the reabsorption of water.

Enteral Routes

Disadvantages:

Adherance : adhere to the instruction of drug intake

1. **The patient must be cooperative (compliant).**
2. **Absorption is variable because of several factors affecting the rate and extent of absorption:**

a) **Vomiting**
b) **Failure of disintegration and dissolution**
c) **First-pass effect**
d) **Drug may be destroyed by gastric acid or intestinal flora.**

Enteral Routes

e) **Food may delay absorption.** 👀 خاصة اللي ببلعه بلع

Lipid-soluble drugs are better absorbed when taken with fatty foods

f) **Alteration in intestinal motility may affect absorption.**

If there is a delay in intestinal motility and the drug is acidic, most absorption occurs in the stomach

g) **Absorption may be affected by splanchnic blood flow.**

Enteral Routes

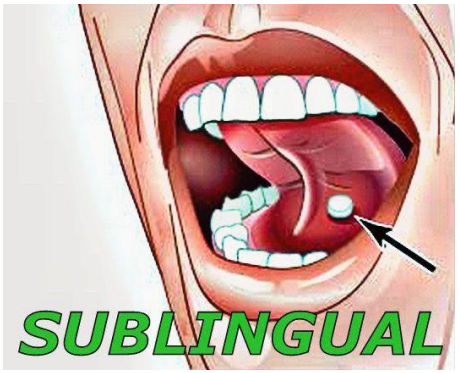
Rapid absorption because the area under the tongue is highly vascular.

Saliva helps disintegrate the tablet, allowing the drug to enter the circulation directly

2. Sublingual route (SL):

- Drug is placed under the tongue.
- Avoids first-pass effect.
- Used when a rapid onset is required – such as in angina pectoris.
- Not commonly used.

That's why the tablet should not be swallowed, because if it enters the stomach, it may undergo the first-pass effect and lose its rapid action



Enteral Routes

This is because drainage from the rectum is split:

Half goes directly to the systemic circulation.

Half goes to the portal circulation →undergoes first-pass metabolism

3. Rectal route (PR):

- Avoids first-pass effect partially (~ 50%). Why?
- Useful in unconscious or vomiting patients. And baby
- Absorption is often irregular, incomplete and unpredictable.
- Can be used for a <u>local effect</u>.
- Used for drugs poorly absorbed from, or unstable in the GIT.
- Used for rapid effect.
- Aseptic technique is not required.

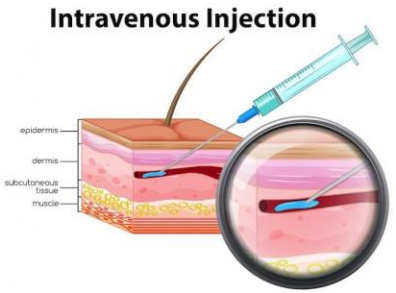
Example:Someone has hemorrhoids so in this case we call it topical administration which means apply the drug to the region to act locally

They are contradictory, but the book presents it this way

Parenteral Routes

Bolus: a single, rapid dose given to the patient, usually over a few minutes.
Infusion: a slow, continuous dose given over a longer period of time, often used in severe cases in the ICU.

1. Intravenous route (IV):



- Bolus vs infusion.
- Only aqueous solutions may be injected IV.
- Rapid onset of action.
- Oily vehicles or those that precipitate blood constituents should NOT be given IV. To avoid cloting
- No first-pass hepatic metabolism, the drug goes first to the right side of the heart, the lung, the left side of the heart, then to the systemic circulation.

عشان حطيتلكوا صورة لكل طريقة ادعولي بدعوة حلوة ◔‿◔

Parenteral Routes

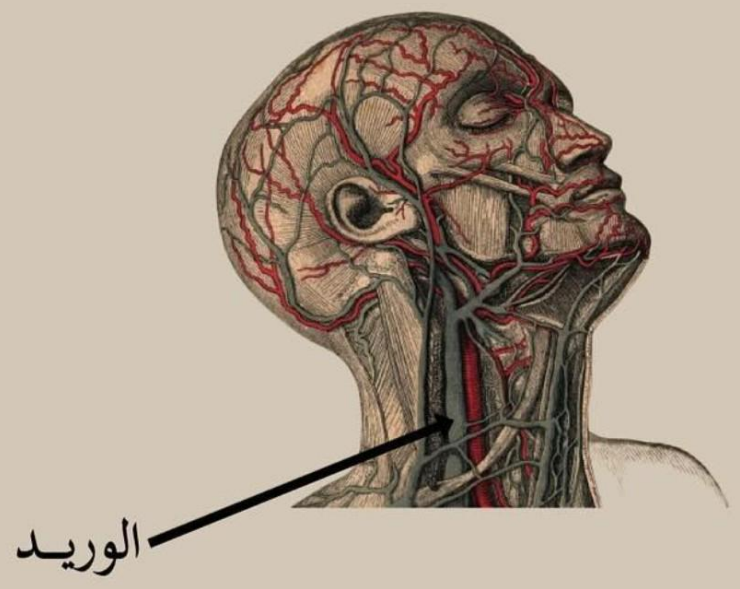
Disadvantages:

1. **Produce high initial concentration of the drug that might be toxic.**
2. **Once injected, the drug is there…??**

Additional Resources:

رسالة من الفريق العلمي:

أرِح فُؤادك
ولا تشكو همّك
لغير الله تعالى ولا
تظنّ أن الله غافل
عنك



وَنَحنُ أَقـرَبُ
إِلَيــهِ مِن حَبلِ
الوَريـــــــــــدِ

We are closer to him than
his jugular vein.

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			