Pharmacokinetics 4

Yacoub Irshaid MD, PhD, ABCP
Department of Pharmacology

Modified by Dima Rafaiah

Zero-Order Drug Elimination

Certain amount is lost per unit time (limited capacity for elimination)

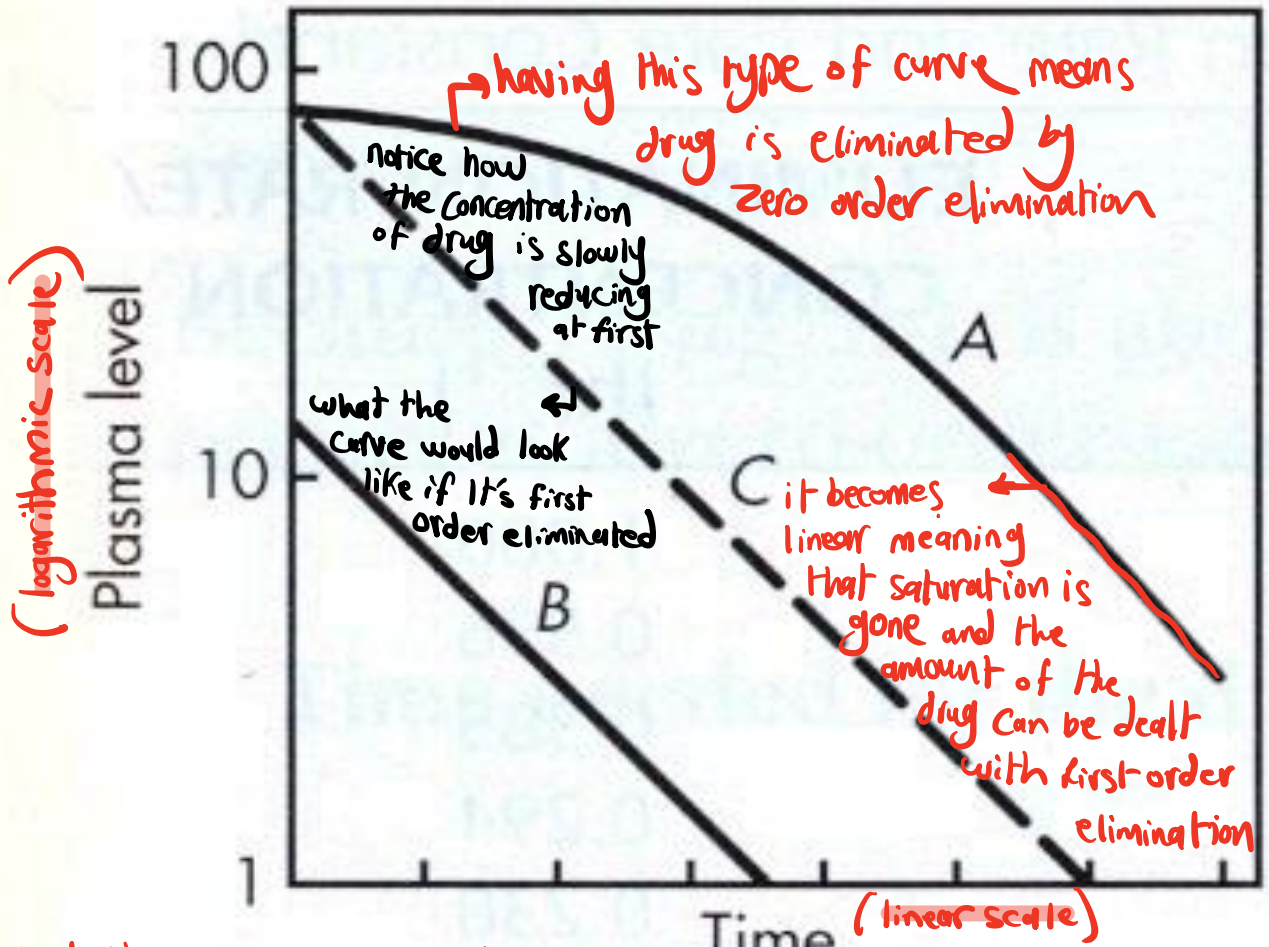
- Also called **Saturable elimination**.
- Occurs with few drugs (aspirin, phenytoin, ethanol, ..).

very important drug in the treatment of certain kinds of epilepsy

- **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.**

- increasing the dose increases accumulation of the drug, half life will be prolonged (That's why it's called saturable)

- Semi-log Scale



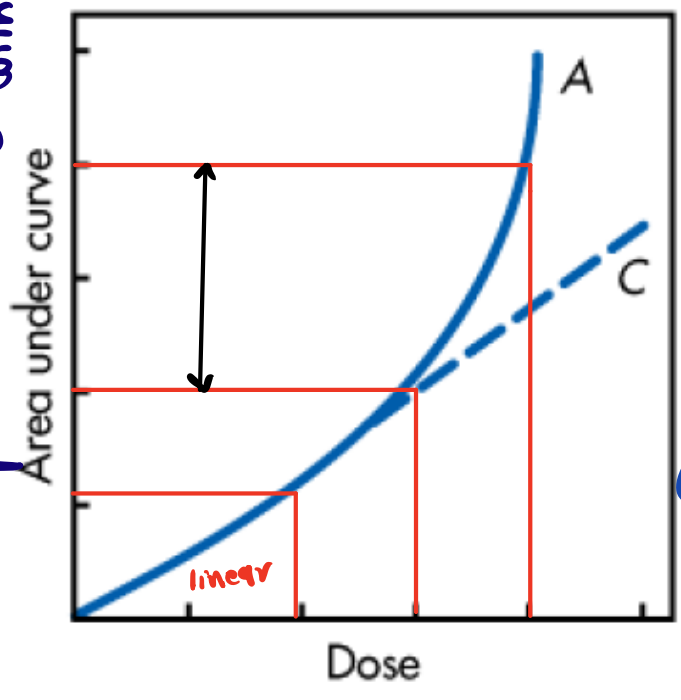
- looking at the curve, when the concentration was high ⇒ elimination is slow
- As the drug drops, the elimination becomes faster until the curve becomes linear

Zero-Order Drug Elimination

Concentration of the drug

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

Where V_{max} is the maximal elimination capacity, and K_m is the drug concentration at which rate of elimination is 50% of V_{max}.



- As shown, at low doses it's linear.
- The increase in the dose of the drug that undergoes zero elimination leads to an out of proportion increase in the area under the curve (out of proportion increase in the plasma concentration of the drug)

ex: if we want to increase the concentration of a certain drug undergoing zero order elimination we can't just increase the dose because it may lead to an out proportion increase in the plasma concentration resulting in toxicity

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

Curve C represent first-order kinetics

First-order

It has a proportional relationship with the concentration of the drug.

As the drug concentration increases the rate of elimination increases

* Concentration-dependent process

The higher - The faster

* As the doctor said a constant proportion (percentage, fraction) is eliminated per unit time

Zero-order

It has limited capacity of elimination, only limited amount of the drug is eliminated

So increasing the conc. of the drug won't increase the rate of elimination

Rate of elimination remains constant irrespective to the drug conc.

* Concentration independent

* A constant amount (milligrams) of the drug is eliminated per unit time

Depending on the blood flow

Flow-Dependent Drug Elimination

first pass effect ↗ metabolism ↘ excretion

- 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 organ is eliminated on first pass of the drug through the organ.
- Rate of elimination is determined by the rate of hepatic blood flow.
- Drugs that have this property are called "high extration ratio" drugs.
- Include morphine, lidocaine, propranolol, verapamil, and others.

we have certain drugs that decreases blood flow to the liver to decrease elimination of these flow dependent drugs

↑ hepatic blood flow ↑ elimination of these drugs

⇒ They are extracted significantly during their passage in the liver

Those examples are not required

Half-Life (t½) of Elimination

It determines the frequency of drug administration within therapeutic range

- 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. (3-5 half lives)
- It is related to first-order elimination rate constant (k) such that:

$k \times t_{½} = 0.693$

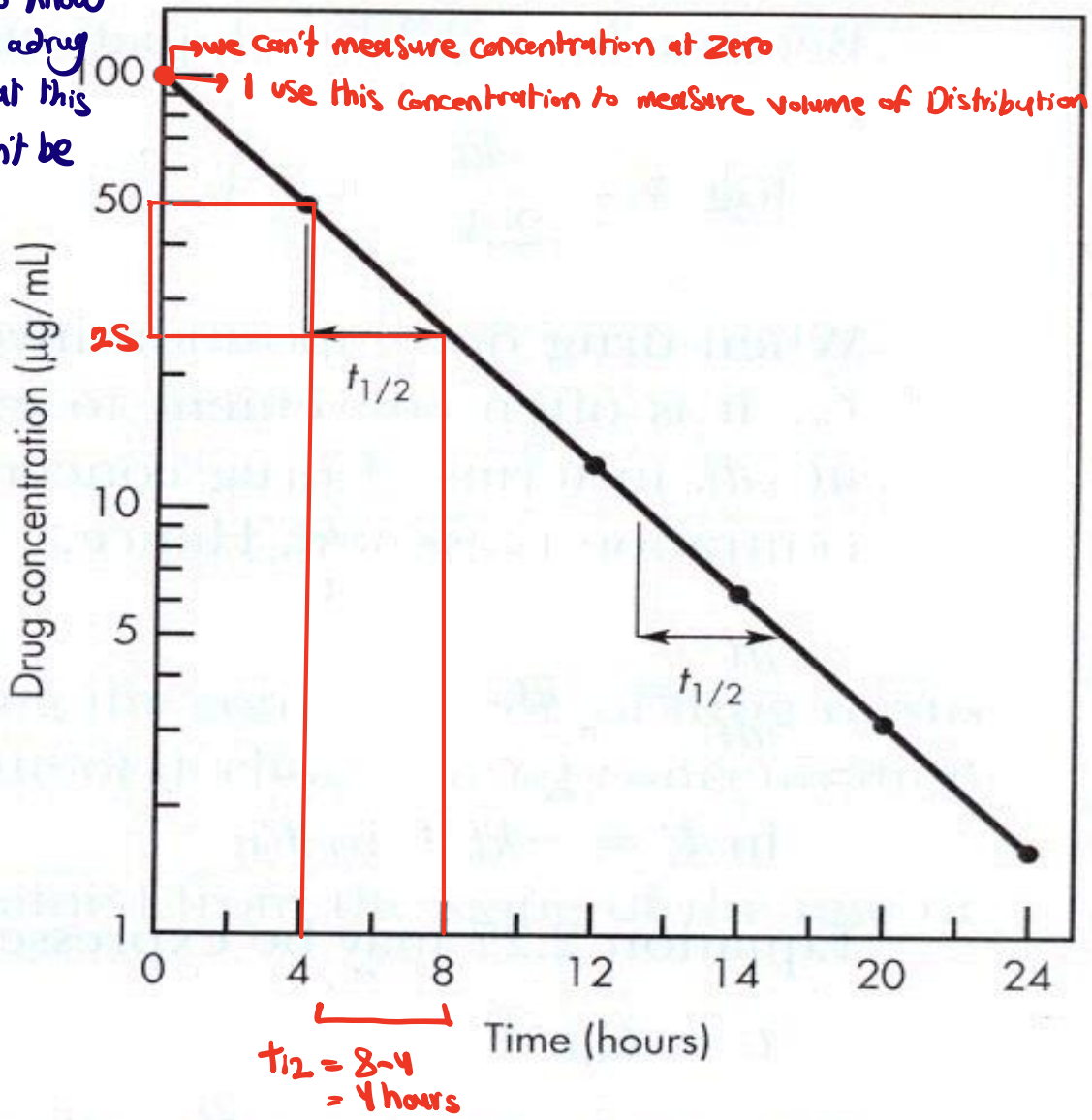
→ for all drugs undergoing first order elimination

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

So it's almost 4 half lives

doesn't apply to zero order since half life is not constant

It's possible to know the half life of a drug by only looking at this curve but it won't be accurate.



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
→ a measure for both elimination and distribution of the drug

CL = k.Vd → v.imp

t½ = 0.693 Vd/CL

while if we say hepatic clearance → elimination by the liver only
renal clearance → elimination by the kidney

"Total clearance" → Both elimination and distribution

Half-Life (t½) of Elimination

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

In the first order, increasing concentration won't increase the half life

We're now able to recognize the 4 parameters of pharmacokinetics

- Volume of Distribution of the drug
- Clearance of the drug
- first order elimination rate (K)
- half life of the drug

Those parameters are extremely important to make the right calculations ending up with the therapeutic dose of the drug the patient needs.

Mind you that those parameters are constant characteristics of a drug under normal conditions.

(ex.) half life of a drug won't change overnight unless you're suffering from a certain disease that should be considered.

Steady-State

of the drug concentration to have the therapeutic effect

- **Steady-state is a condition achieved following repeated drug administration as occurs in clinical practice.** "أثناء العلاج"
- **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.** when drug is administered orally

- At the peak of Concentration (For a single dose) → The rate of absorption = The rate of elimination
- At the peak of steady state → The dosing rate = The rate of elimination

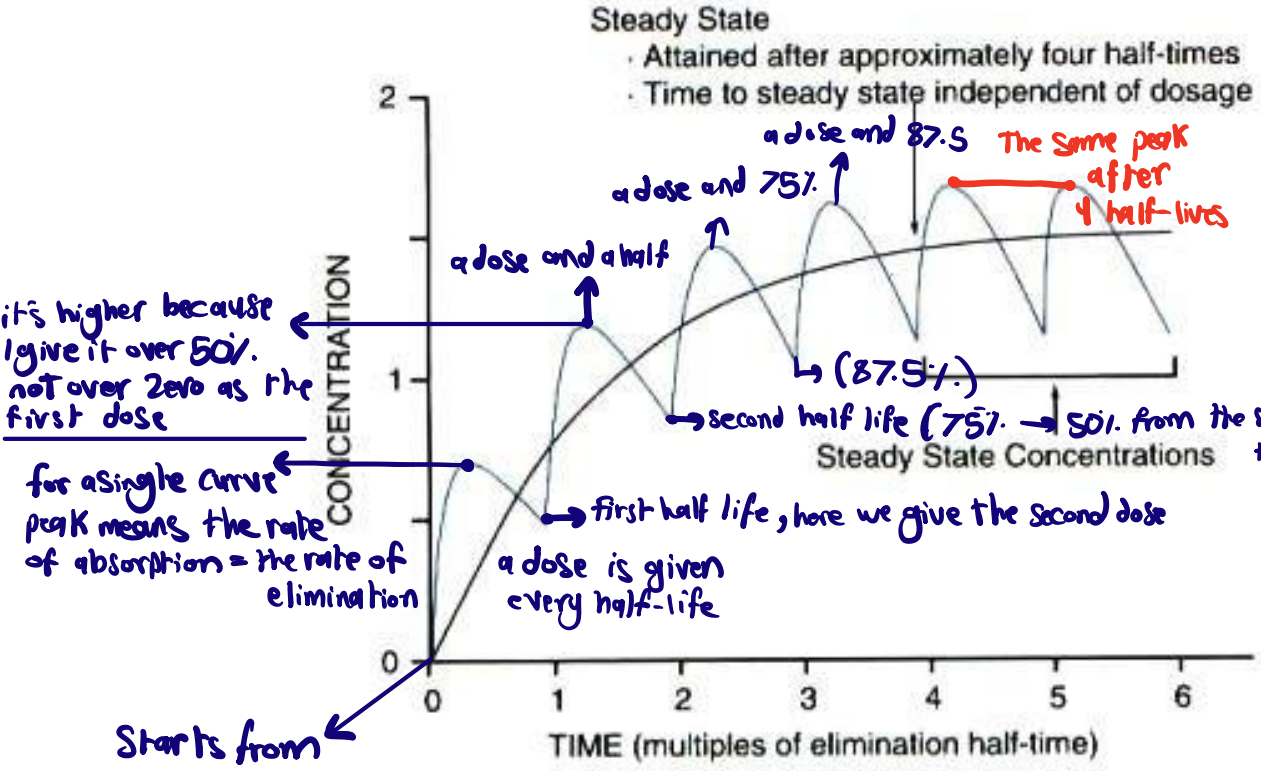
Steady-State

2 months → 8 months
48 hours → 8 days
24 hours → 4 days

(ex.) a drug with half life of 2 hours would reach steady-state after 8 hours

- **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.**

Site of administration → oral



As shown with continuous dosing the concentration increment decreases until reaching the steady state

it's higher because I give it over 50% not over zero as the first dose

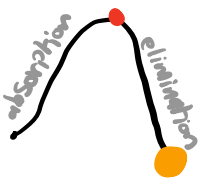
for a single curve peak means the rate of absorption = the rate of elimination

Starts from zero so it's given orally

The curve won't be the same if the drug is administered IV

للتوضيح :

كل جرعة منعطيها بتمر بمرحلتين absorption و elimination



- عند القمة ← Absorption = elimination

- هون بكون مرت الـ Half life يعني راح ٥٠٪ من تركيزو

فعشان هيك احنا منحاول نوصل Steady state منروح منعطي جرعة تانية بتمر بنفس المرحلتين (absorption , elimination)

الفرق انو القمة هون بيكون تركيز الدوا عندها عبارة عن الجرعة التانية كاملة + نص الجرعة اللي مرت بأول Half life

صح؟ لما نوصل عند تاني Half-life الجرعة اللي رح تنزل للنص ← نص الـ ٥٠٪ ← ٢٥٪ ضل ٢٥٪

الجرعة التانية رح تنزل للنص ← نص الـ ١٠٠٪ ← ٥٠٪

يعني اديش راح يضل ٧٥٪ من تركيز الدوا اللي جاي من الجرعتين

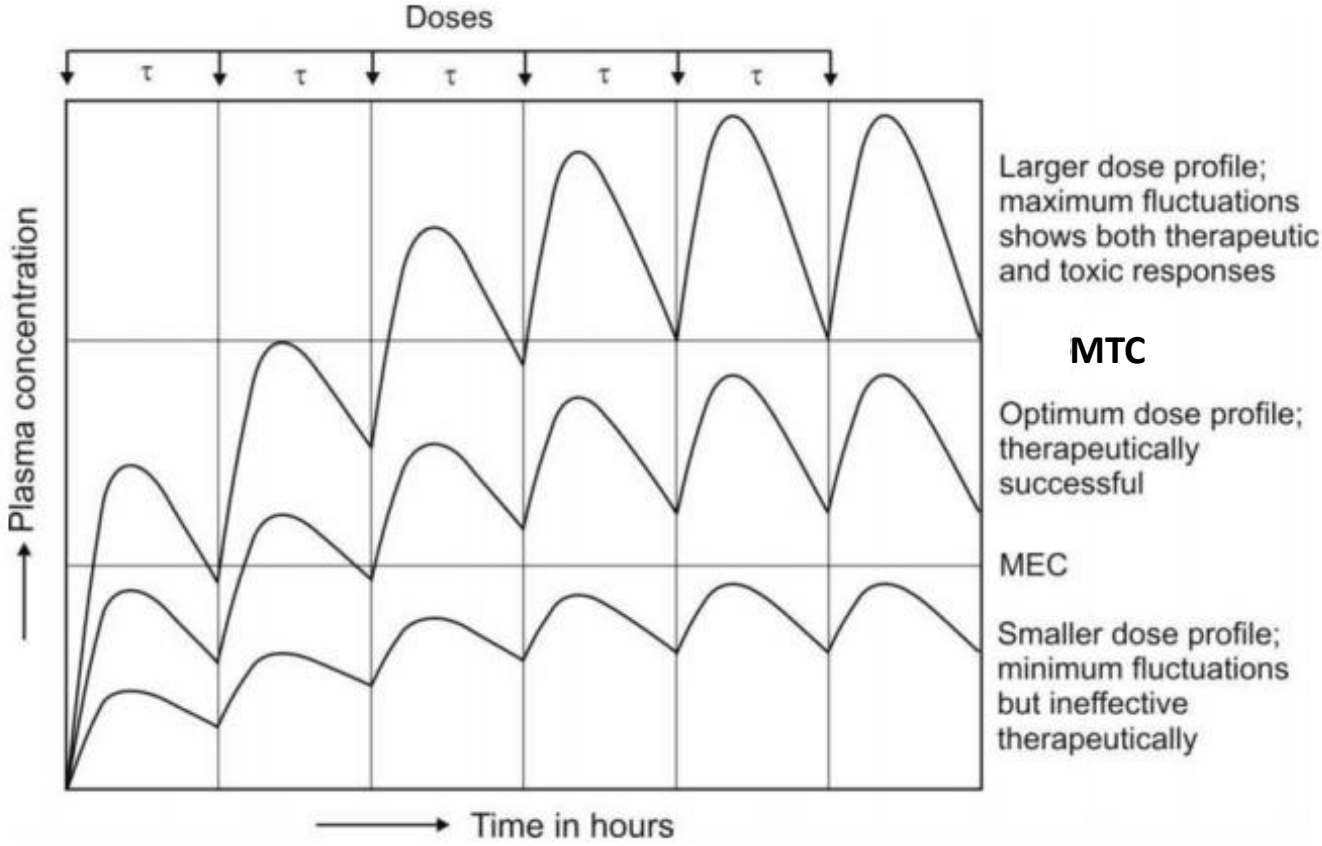
لما ييجي للجرعة التالتة ونوصل لـ peak رح اعتبر عندي جرعة تالتة + نص الجرعة ٢ + نص نص الجرعة الأولى (١٠٠ + ٥٠ + ٢٥) = جرعة و ٧٥

وهيك كل ما تخلص Half life منزل نص من كل جرعة

وعند كل قمة منزيد جرعة كاملة مع اللي عم يضل من الجرع اللي قبل

لحد ما تصير الزيادة على كل جرعة جديدة صغيرة كتير وهون منوصل لـ Steady state

يارب تكون وضحتو


Doses
τ
τ
τ
τ
τ
Plasma concentration
Time in hours
Larger dose profile; maximum fluctuations shows both therapeutic and toxic responses
MTC
Optimum dose profile; therapeutically successful
MEC
Smaller dose profile; minimum fluctuations but ineffective therapeutically

first order kinetics

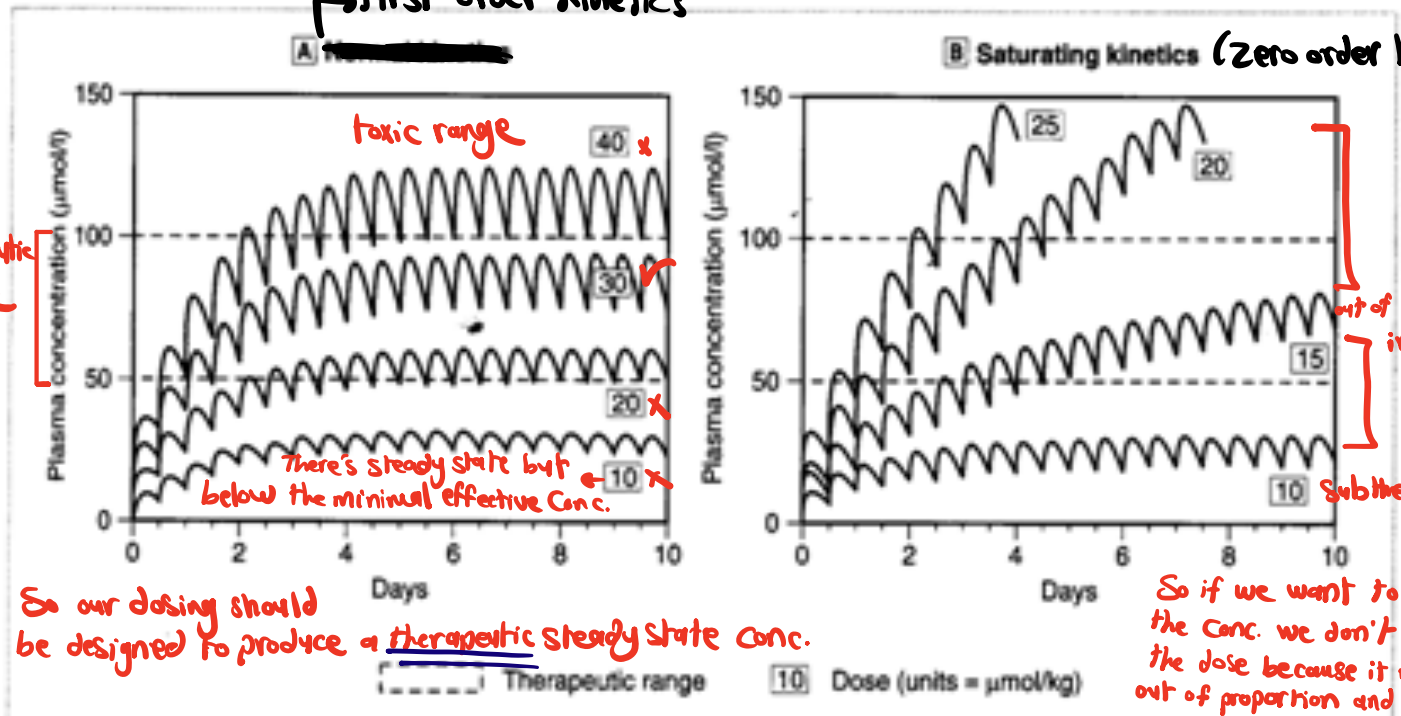


Fig. 5.13 Comparison of non-saturating and saturating kinetics for drugs given orally every 12 hours. A The curves show an imaginary drug, similar to the antiepileptic drug phenytoin at the lowest dose, but with linear kinetics. B The curves for saturating kinetics are calculated from the known pharmacokinetic parameters of phenytoin (see Ch. 36). Note (i) that no steady state is reached with higher doses of phenytoin and (ii) that a small increment in dose results after a time in a disproportionately large effect on plasma concentration. With linear kinetics the steady-state plasma concentration is directly proportional to dose. Curves were calculated with the 'Sympak' pharmacokinetic modelling program written by Dr J G Blackman, University of Otago.

Loading Dose (LD)

A function of volume of distribution

- **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).**

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

desired steady state therapeutic concentration

- It can cause toxicity, in this case the loading dose is divided and given in short intervals.

Maintenance Dose (MD)

A function of clearance of the drug

- **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.**

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

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

Case Scenario

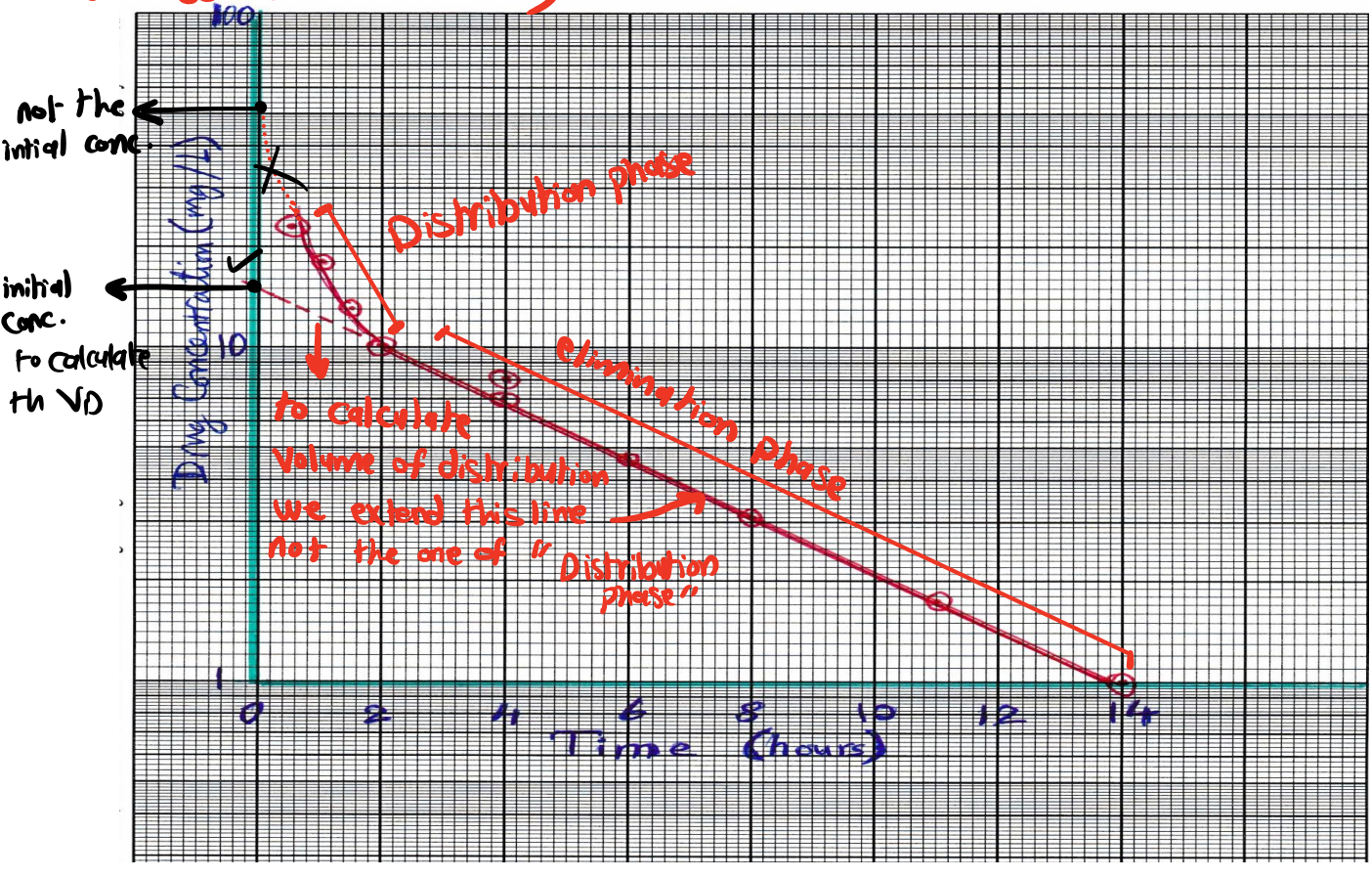
- **A volunteer was given a single 400 mg of a drug by IV injection. Serial blood samples were taken to analyze for drug level and construct a plasma concentration-versus-time curve.**

Results

Time (hours)	Drug concentration (mg/L)
0.5	23
1	18
1.5	13
2	10
4	7
6	4.7
8	3.1
11	1.75
14	1

The following semi-log plot of plasma concentration-versus-time was obtained

Because it's administered IV, it won't start from zero.



Q1

Which of the following is the approximate apparent volume of distribution of the drug?

A. 5 L
B. 10 L
C. 25 L
D. 50 L
E. 100 L

Q2

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

A. **1.5 hours**
B. **3.5 hours**
C. **5.5 hours**
D. **7.5 hours**
E. **9.5 hours**

Q3

Which of the following is the first-order elimination rate constant of the drug?

A. **0.0385 / hour**
B. **0.0770 / hour**
C. **0.1155 / hour**
D. **0.1540 / hour**
E. **0.1925 / hour**

Q4

Which of the following is the clearance of this drug?

A. **1 L/hour**
B. **2 L/hour**
C. **3 L/hour**
D. **5 L/hour**
E. **10 L/hour**

Q5

What is the maintenance dose every 24 hours if the steady-state therapeutic concentration of the drug is 10 mg/L?

A. **100 mg**
B. **500 mg**
C. **750 mg**
D. **1000 mg**
E. **1200 mg**

Q6

Does this drug require a loading dose?

A. **Yes**
B. **No**
C. **I do not know**

If the answer is yes, calculate the loading dose.