Doctor 021

PHARMACOLOGY

Sheet no. 9

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pharmacokinetics (4)

First Order Drug Elimination

- **It occurs when the rate of drug elimination is directly proportional to the amount of drug in the body.**
  - As the drug concentration increases, the elimination increases (Concentration-dependent)
- **Occurs with many drugs at therapeutic concentrations.**
  - Which is good, because sometimes drug accumulation is not significance.
- **A constant fraction of the drug is eliminated**
  - Constant Percentage of the drug concentration is eliminated per unit time

(no saturation of the elimination process)

- EX: a constant fraction is: 0.1 mg and assume having 100mg of the drug, so 10 mg will be eliminated per unit time.

if there is 1000 mg in body, the eliminated amount is 100 mg

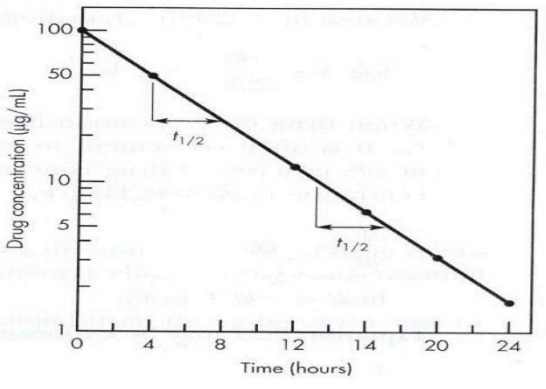
if 10000 mg …… 1000mg per unit time

the more amount of the drug , the more eliminated rate due to a constant half life.

- **The elimination rate constant is designated as K, and its units are reciprocal time (1/time)meaning fraction per unit**

NOTES:

- This is a Semi-log plot linear scale.
- When the drug is first order eliminated you would see straight line as shown.
- You can notice that a drug undergoing first order elimination has a constant half-life (which the time required for the drug concentration to drop to the half and here it's 4)



Zero-Order Drug Elimination

- **Also called Saturable elimination.**
  - So it has limited capacity for elimination.
- **Occurs with few drugs (aspirin for small doses of heart diseases,phenytoin for epilepsy, 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.**

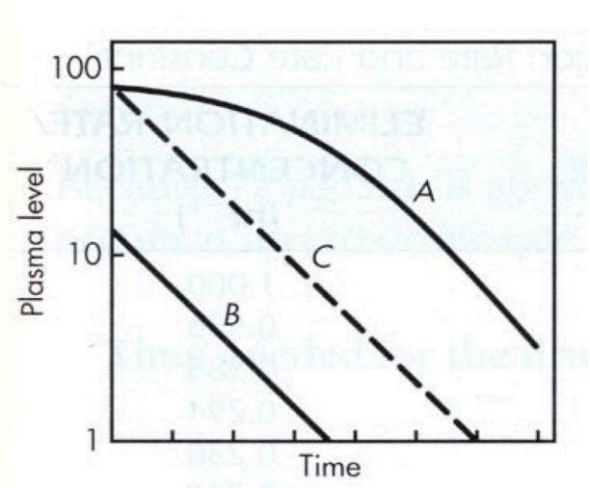
Here the drug has prolonged half-life (not fixed)

Zero—constant amount

First –constant fraction

❖ **here again with the semi log scale:**

NOTES:



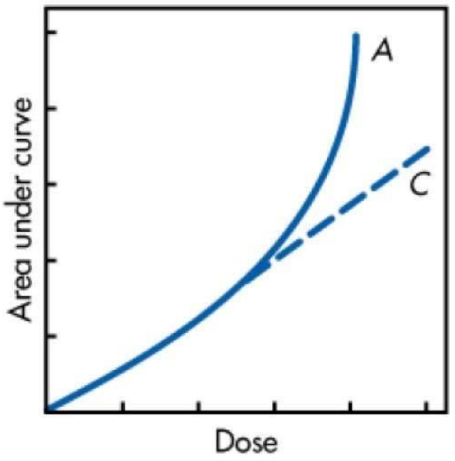
- Curve A represents zero order elimination, you can notice the difference between it and curve C that represents the same drug if it was first order eliminated.
- As shown the drug concentration that is zero order eliminated is reducing slowly at higher concentrations (because of the limited capacity).
- As the time progresses, notice how elimination is becoming faster and the curve linear (here the saturation is gone, and the drug is first order eliminated).

- **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}.**

Curve C represent first-order kinetics

NOTES

- After following concentration with time, we can get area under their curve.
- At low doses, its linear.
- As the time progresses, the increase in the dose of the drug that undergoes zero order elimination leads to an out proportion increase in the AUC (out of proportion increase in the plasma concentration of the drug)



- Conclusion: 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

Flow-Dependent Drug Elimination (fast first order)

- Some drugs are cleared very rapidly by the organ ofelimination (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 extraction ratio" drugs. Include morphine, lidocaine, propranolol, verapamil, and others.

❖ It's a Very fast elimination, that depends on the blood flow.

Some drugs are used to reduce blood flow to the liver, consequently they will reduce the elimination of these drugs.

Remember that there are abundant enzymes that metabolize drugs in the liver , so anything that reaches the liver will be eliminated.

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%.

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

- **In this case it is constant, and not related to dose.**
- **After ~ 4 half-lives, most of the drug wilbe eliminated from the body.**
- **It is related to first-order elimination rate constant such that:**

k x t½ = 0.693

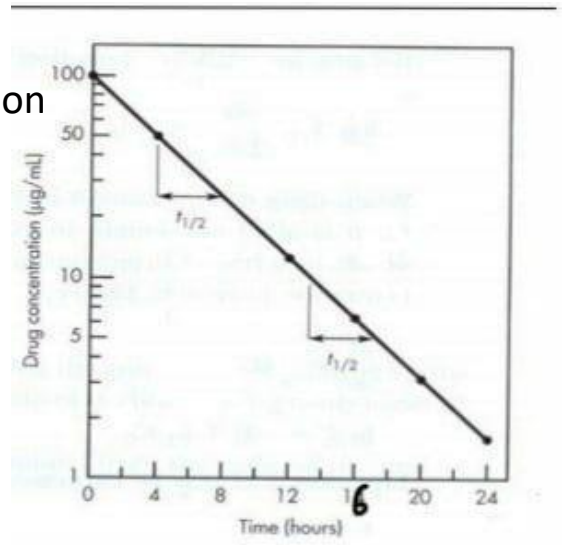
- k unit is per time, half-life unit is time, so this total equation has No unit.

❖ **EX.** assume that we have a drug undergoing zero order elimination, and we gave a 100ml dose when the body capacity to eliminate the drug is 5ml per hour, so basically, we need ten hours to reach 50 ml concentration, thus half-life is 10 hours. Now assume that we gave the patient 200 ml, so we need 20 hours to reach 100 ml concentration.
Meaning that increasing the concentration will increase the half-life and vice versa.

➢ But why this doesn't apply to zero order elimination?

✓ Because it eliminates a constant amount not a constant ratio like the first order.

➢ **We can calculate from this picture:**



1. to calculate $t_{1/2}$: after 4 hour the concentration is 50 ml. as the time progress to 8 hours we reach half of that concentration (25ml) so t1/2 = 8-4=4 hours. Try doing the same thing to any other points on the curve and the half time would still be 4 hours. SOOO, it is a first order elimination because the half-life is constant

2. for calculating the Vd:

Vd = amount of the drug / plasma concentration

The plasma concentration is at time zero but we can't calculate it so we calculate multiple points

And since the first order is linear plot so we draw the multiple points and extend the plot backward until we reach time zero

3. for calculating the clearance:

Cl = (.693/ half-lives)

Half-life = .693*Vd/cl

K* half-life = .693 ..... thus k = .693/half life

Cl = (.693/half-life)*Vd ..... Half-life = .693* Vd/cl

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

CL = k. Vd

t½ = 0.693 Vd/CL

remember, the clearance is when the drug distribute from the blood to tissues or go out of the body.

This equation indicates the total clearance which is both elimination and distribution.

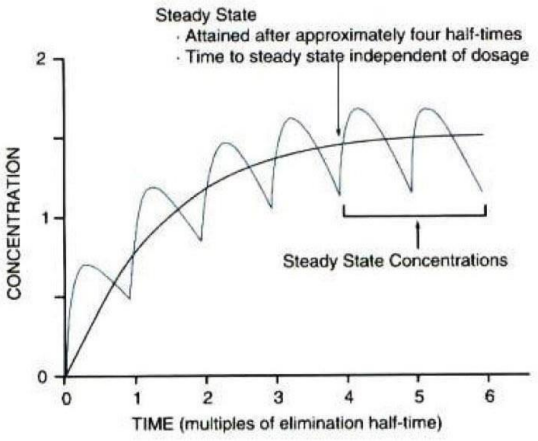
Half-Life (t½) of Elimination

- **It is related to dose and plasma concentrationfor drugs undergoing zero-order kinetics and isNOT constant.**
- **The higher the concentration, the longer the half-life of elimination and vice versa.**

Steady state

- **Steady state is a condition achieved followingrepeated 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. Concentration of the drug in the body becomes constant because the drug administration is equal to the drug elimination (firstorder)**
- **At steady state, a constant peak, trough, andaverage drug concentrations are achieved.**
- **Steady state is achieved after approximately 4half-lives of repeated drug administration. 50% of SS is achieved after one half-life of administration.**

❖ if the half-life is one day the steady state occur after 4 days how ? after one day we achieve 50% of the concentration, after 2 half-lives we achieve 75% of concentration, after 3 half-lives we achieve 87.5% of steady state concentration, after 4 half lives we achieve 93.75% of the steady state concentration.



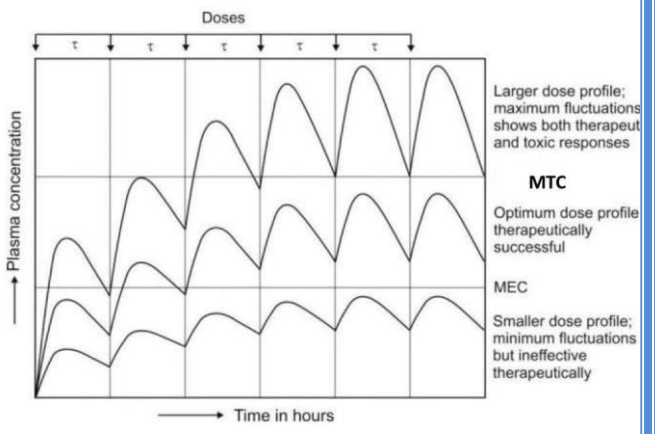
- To reach the steady state we need a constant peak, trough, and average.We enter the steady state after 4 half-lives how?

- Let's assume that we gave first dose of 100ml and the half-life for the drug is 4hours, so the concentration now is 150 ml, after 4 hours the concentration will decrease to 87.5 ml approximately 90 ml we gave another dose the concentration become 190 after 4 hours will decrease to 95 approximately 100 ml give another dose it becomes 200 ml will decrease to 100 after 4 hours and so on, **We reach a constant condition called a steady state concentration**

- **Our aim during drug therapy is to attain a steady-state drug concentration (Css) within thetherapeutic range, but NOT subtherapeutic or toxic**.

- **MTC: minimal toxic concentration**
- **MEC: minimal effective concentration**

- We can enter the ss with a small dose, but it won't be effective because it is below the MEC. Also, we can enter the ss with a high dose, but it would be toxic.



A: first order kinetic

B: zero order kinetic (saturating kinetics)

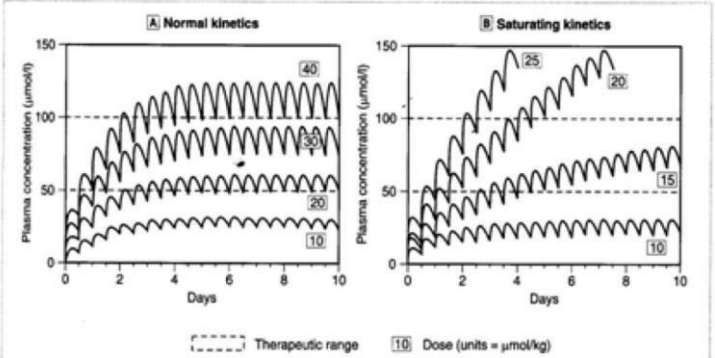


Fig. 5.13 Comparison of non-saturating and saturating kinetics for drugs given orally every 12 hours. A The curves show an imaginary drug, similar to the antiepileptic drug phenytoin at the lowest dose, but with linear kinetics. B The curves for saturating kinetics are calculated from the known pharmacokinetic 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.

❖ **Again, we are trying to reach the "therapeutic" steady state by giving the right repeated dose. So, I don't want to reach a toxic or subtherapeutic ss.**

Now let's follow the two curves.

A. First thing to be noticed is that the increase in the dose is proportional to the plasma concentration.

- A 10 mg dose reached ss but it's beneath minimal effective concentration (the therapeutic range is between 50-100).
- Doubling the dose give us double the concentration (because it's first order elimination) but still it didn't reach therapeutic ss.
- 30 mg dose was just perfect, and it reached the therapeutic ss.
- 40 mg dose reached a toxic steady state so it's not the right one.

B. Moving to the zero-order kinetics, we will notice that the increase in the dose leads to an out proportion of the plasma concentration (doubling the dose doesn't result in doubling the plasma concentration)

  - As shown, none of the doses given have reached ss.

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

- CSS desired: desired steady state therapeutic concentration.

❖ Of course, loading dose of certain drugs may lead to toxicity, in this case we divide the loading dose and give it in short intervals.

❖ For example, if we have 900 ml dose, we divide itinto 300 ml every 3 hours in the same day to avoid the 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**

. MD = CL . $Css_{desired}$

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

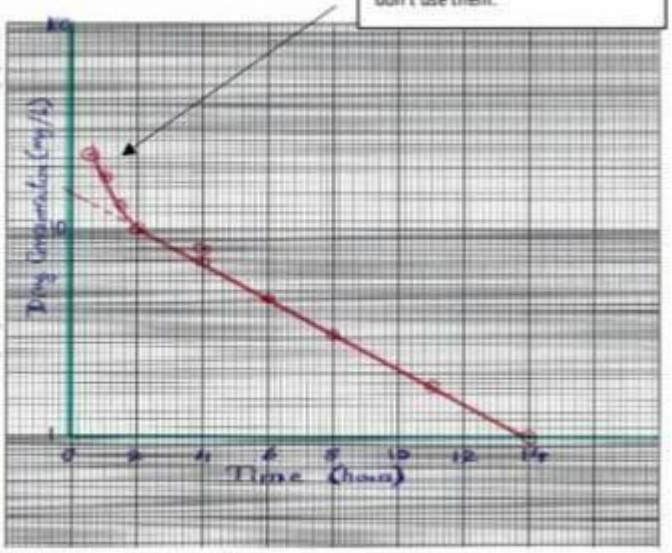
Simply it's the daily dose that we give the patient to compensate the loss of the drug so it's function of clearance.

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: **the beginning of curve is distribution not elimination**

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



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

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 9

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.

1.C

2. B

3. E

4. D

5. E

6. C

Q1:- Vd = AB / Cp

- AB = 400 mg
- Cp ⟵ امتداد الخط المستقيم في الرسمة = 15 mg/L
- Vd = 400 / 15 ≈ 25 L

Q2:- half life ⟵ من الرسمة

from 10 mg/L to 5 mg/L ≈ 3.5 hours

Q3:- $K = \frac{0.693}{\text{half life}} = \frac{0.693}{3.5} \approx 0.1925/\text{hour}$

Q4:- Cl = Vd · K = 25 L x 0.1925 /hour
= 5 L /hour

Q5:- MD = Cl x Css = 5 L/hour x 10 mg/L
x 24 hour
= 1200 mg

Q6:- (ii) السؤال كان في أي شخص

If yes, LD = Vd x Css
= 25 L x 10 mg/L
= 250 mg