Pharmacology

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Pharmacokinetics part II

4- Excretion: the kidney is the most important organ for excretion of drugs. The lungs and sweat usually play a minor role.

Clearance:

Clearance (CL) relates the rate of elimination to the plasma concentration.

$$CL = \frac{\text{Rate of elimination of drug}}{\text{Plasma concentration of drug}}$$

Unit= (Volume per unit time)

For drugs eliminated with first-order kinetic, clearance is a constant; that is, the ratio of rate of elimination to plasma concentration is the same regardless of plasma concentration. Note that for drugs eliminated with zero-order kinetics, clearance is not constant.

A) First-order elimination:

The term first order elimination indicates that the rate of elimination is proportional to the concentration (i.e., the higher the concentration, the greater the amount of drug eliminated per unit time). The result is that the drug's concentration in plasma decrease exponentially with time.

Drugs with first-order elimination have a characteristic half-life of elimination that is constant regardless of the amount of drug in the body. The concentration of such a drug in blood will decrease by 50% for every half-life. Most drugs in clinical use demonstrate first-order kinetics.

B) Zero-order elimination:

The term zero-order elimination implies that the rate of elimination is constant regardless of concentration. This occurs with drugs that saturate their elimination mechanisms at concentrations of clinical interest. Such drugs do not have a constant half-life. This is typical of ethanol and phenytoin and aspirin at high therapeutic or toxic concentration.

First order

1. ↑Plasma drug concentration→ ↑rate of drug metabolism.
2. Rate of metabolism is proportional to drug concentration.
3. Constant proportion of drug eliminated per time.
4. Clearance constant.
5. Half-life is constant(time to metabolize 50% of drug)
6. Example :most drug at most doses.
7.

Time(hr)	Plasma conc.	Rate of elimin.
0	8 mg/l	4
1	4	2
2	2	1
3	1	0.5

Zero order

1.↑plasma drug concentration →no↑ rate of metabolism.

2.Rate of metabolism becomes independent of drug concentration. Rate of drug metabolism constant.

3.constant amount of the drug eliminated per time.

4.clearance not constant.

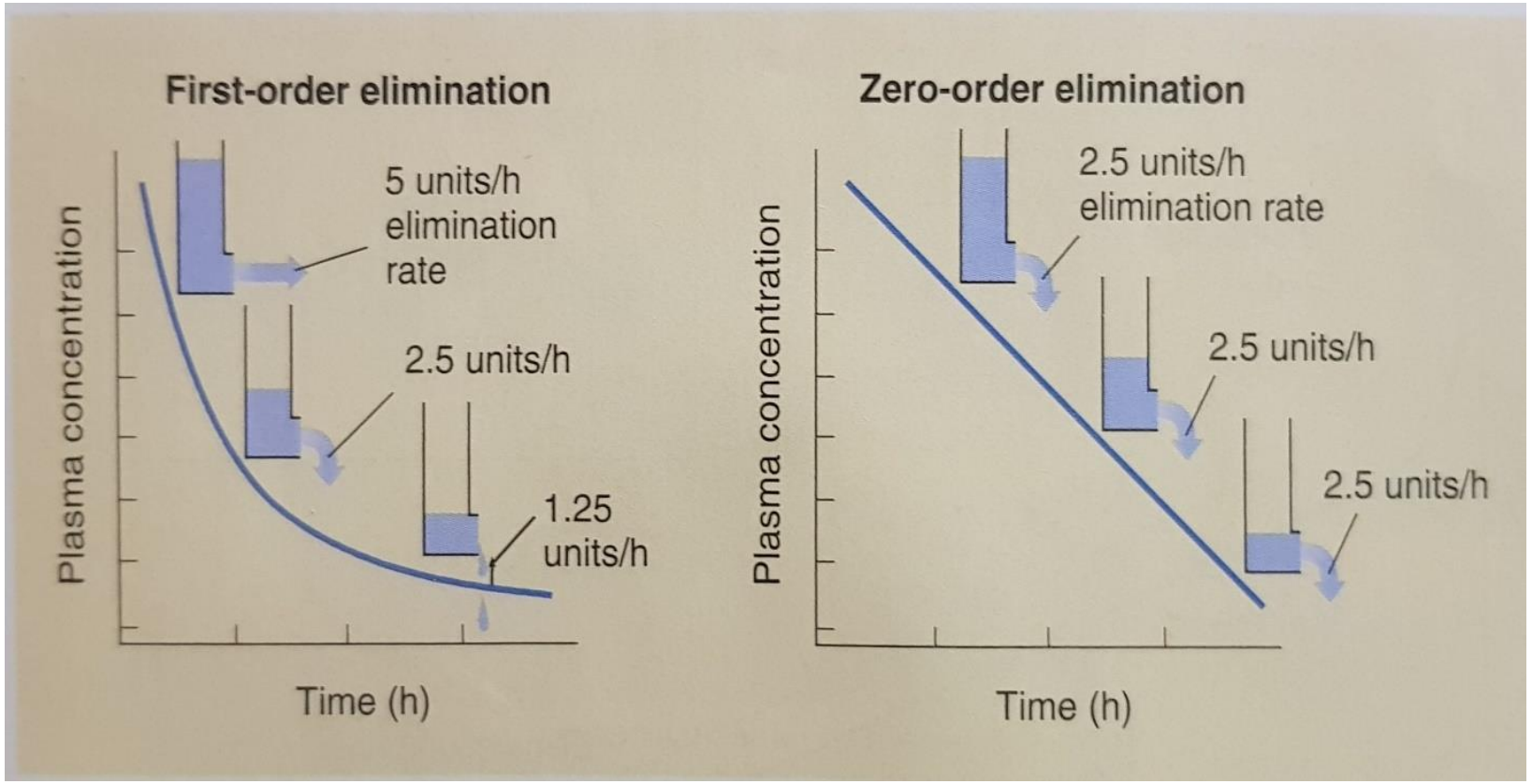
5. half-life not constant.

6.Aspirin,Phenytoin.

7.

Time(hr)	Plasma conc.	Rate of elimin.
0	8	2 mg/l/hr
1	6	2
2	4	2
3	2	2

Fig 1-3: comparison of first- order and zero-order elimination



Half-life (t ½): is the time required to change the amount of drug in the body by one-half during elimination (or during constant infusion). It is a derived parameter, completely determined by Vd and CL. Like clearance, half-life is constant for drugs that follow first-order kinetics.

$$t_{½} = \frac{0.693 \times Vd}{CL}$$

(unit = time)

Half-life (t ½):

- Drugs or substances that have a shorter half-life tend to act very quickly, but their effects wear off rapidly, meaning that they usually need to be taken several times a day to have the same effect.
- Drugs with a longer half-life may take longer to start working, but their effects persist for longer, and they may only need to be dosed once a day, once a week, once a month, or even less frequently.
- From half-life estimate the duration of action for drug.

  (6 x half-life) (duration of action of the drug)

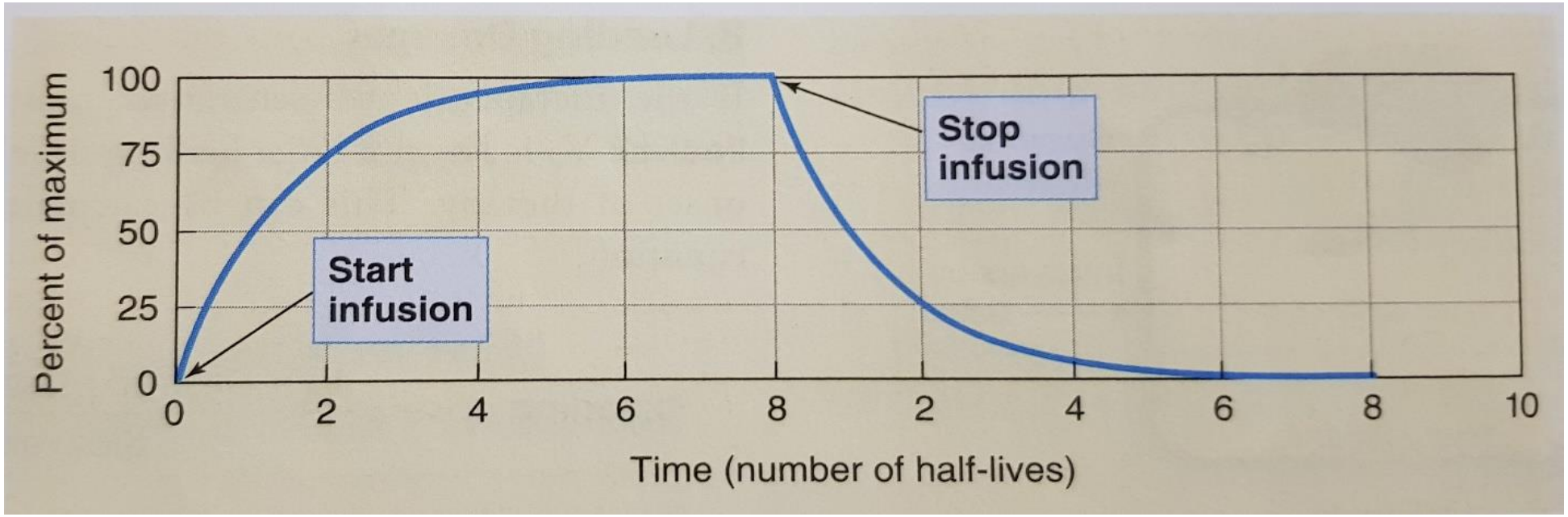


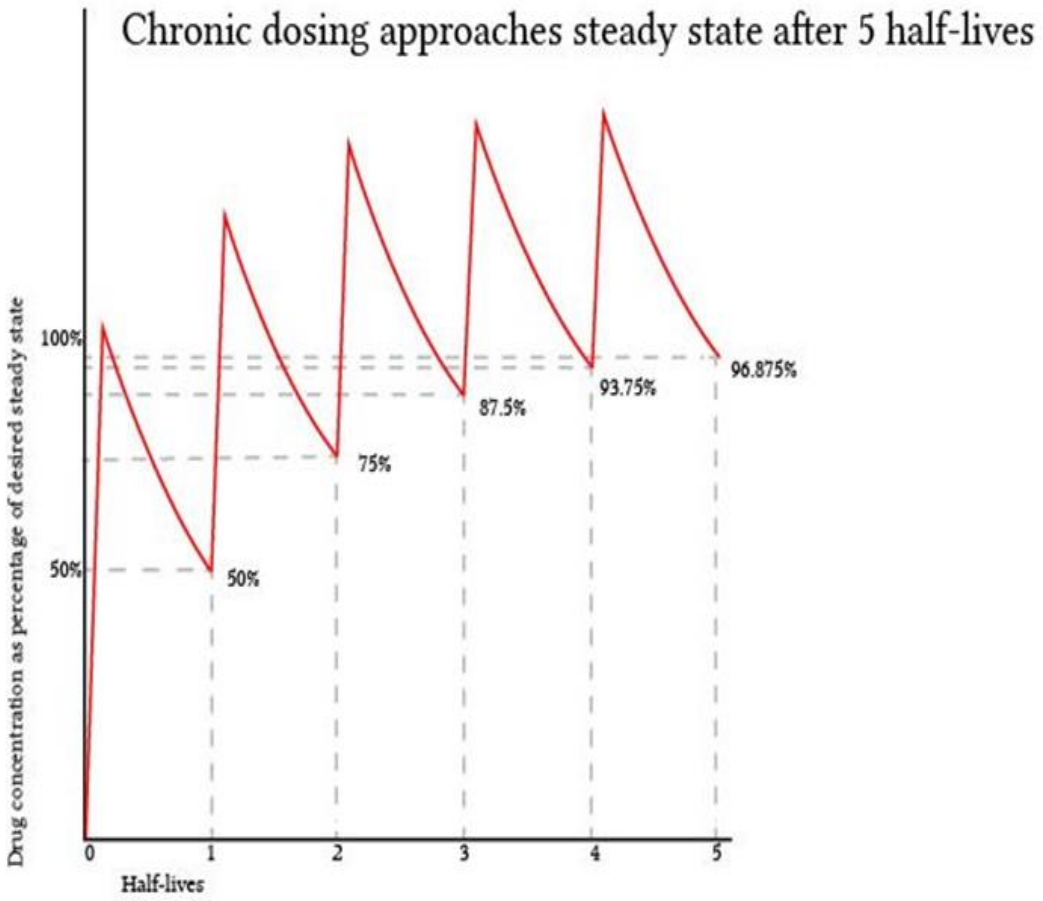
Fig 1-4:plasma conc.(plotted as percent of maximum)of adrug (t1/2 1hr)given by constant intravenous infusion for 8 half-lives and then stopped . the conc. Rises smoothly with time and always reaches 50% of steady state after 1 half-life,75% after 2half-lives, 87.5%after 3 half-lives, and so on. The decline in conc. After stopping drug administration follows the same type of curve :50%is left after 1half-life, 25%after 2 half-lives , and so on . this approach to steady state on both increasing and decreasing limbs of the curve is characteristic of drugs that have first - order kinetics

Steady state plasma concentration: when the rate of drug eliminator is equal to the rate of drug administration such plasma & tissue levels remain constant.

steady state of drug reach after (5-6 half-life)

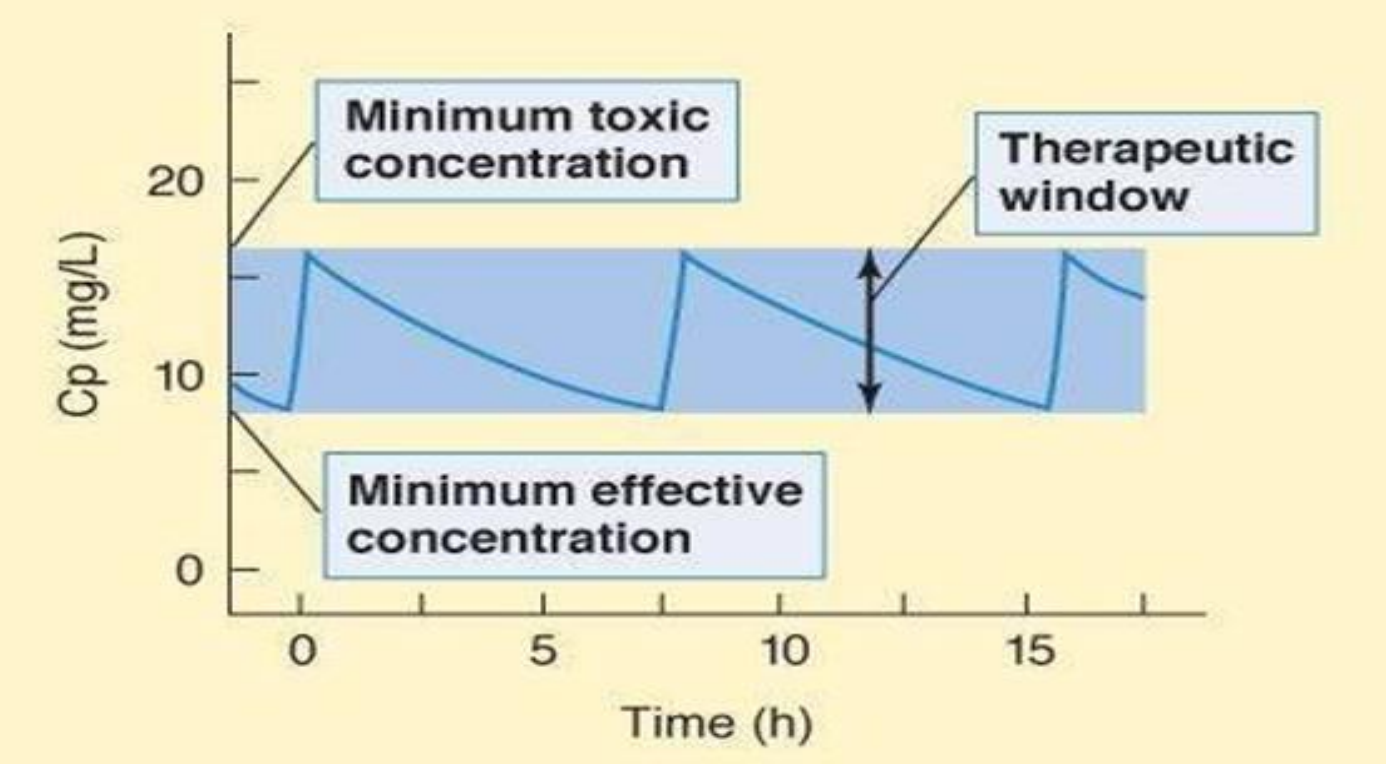
It takes about 5 half-lives for a drug to be roughly 97% eliminated. (50%, then 75% then 87.5% then 93.75% then 96.875%).

In regular doses, drug concentration achieves a steady state in steps, but the end result is the same - the plasma drug concentration reaches a point at which the dose rate and the clearance rate are equal after about five half-lives.



• **Therapeutic window:** is the safe range between the minimum therapeutic concentration and the minimum toxic concentration of a drug. These data are used to determine the acceptable range of plasma levels when designing a dosing regimen. e.g. therapeutic plasma conc. of theophylline 8 mg/L and toxic effect observed at 18 mg/L, Therapeutic window 8-18 mg/L. Fig.1-5

Figure 1-5: The therapeutic window for theophylline in a typical patient.



Dosage regimens: is a plan for drug administration over a period of time. An optimal dosage regimen result in the achievement of therapeutic levels of the drug in the blood without exceeding the minimum toxic concentration. To maintain the plasma concentration within a specified range over long periods of therapy, a schedule of maintenance doses is used. If it is necessary to achieve the target plasma level rapidly, a loading dose is used.

Maintenance dose: Drugs are generally administered to maintain a steady state plasma concentration within the therapeutic window.

$$\text{Dosing rate} = \frac{\text{Clearance (CL)} \times \text{(Desired plasma conc.)}}{\text{Bioavailability}}$$

Loading dose: Sometimes rapid obtainment of desired plasma levels is needed, a large loading dose may be needed at the onset of therapy.

$$\text{Loading dose} = \frac{\text{Vd} \times \text{Desired plasma conc.}}{\text{Bioavailability}}$$

- for drugs with long half-lives, it may be desirable to administer a loading dose that promptly raises the concentration of drug in plasma to the target concentration

Adjustment of dosage when elimination is altered by disease:

Renal disease or reduced cardiac output often reduces the clearance of drugs that depend on renal function. Alteration of clearance by liver disease is less common but may also occur. Impairment of hepatic clearance occurs (for high extraction drugs) when liver blood flow is reduced, as in heart failure, and in severe cirrhosis and other form of liver failure. The dosage in a patient with renal impairment may be corrected

Protein binding:

• A drug's efficiency may be affected by the degree to which it binds to the proteins within blood plasma. The less bound a drug is, the more efficiently it can traverse cell membranes or diffuse. Common blood proteins that drugs bind to are: Albumin, lipoprotein, glycoprotein, and α, β, and γ globulins.

• A drug in blood exists in two forms: bound and unbound:

Protein + drug ⇄ protein-drug complex.

• Unbound fraction which exhibit pharmacologic effects and may be metabolized and or excreted.

• Bound drug is have no action

Factor affecting on the plasma protein binding :-

1-displacement of one drug by another drug ex.:aspirin and warfarin →aspirin displace the warfarin due to high affinity to plasma protein→high free active warfarin →↑ the toxicity of warfarin.

2.↓in the albumin plasma protein due to liver disease lead to ↑the free active drugs→ ↑ toxicity

Thank you