



Pharmacokinetic concepts and dosing terminology

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Intended learning outcomes (ILOS):

Interpret the fundamental principles of pharmacokinetics

Recognize dosing terminology

Discuss the difference between therapeutic index and window

Fundamental Principles of Pharmacokinetics

- To treat a certain disease, we need to **maintain a steady state concentration (C_{ss})** or constant drug level.
- To maintain (C_{ss}) :
(rate of drug administration = rate of drug elimination)
- The most accurate way to do this is with **a constant intravenous infusion**, but an attempt to maintain an approximate steady state **can be reached with repeated doses.**

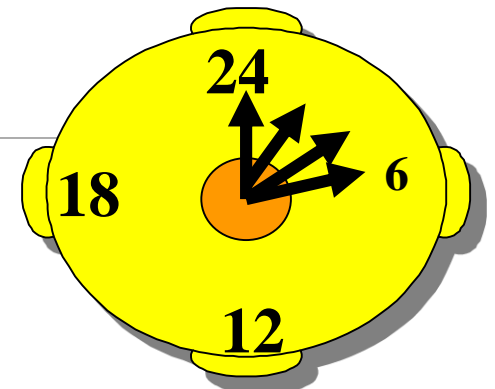
Pharmacokinetic Parameters

Plasma half life ($t_{1/2}$)

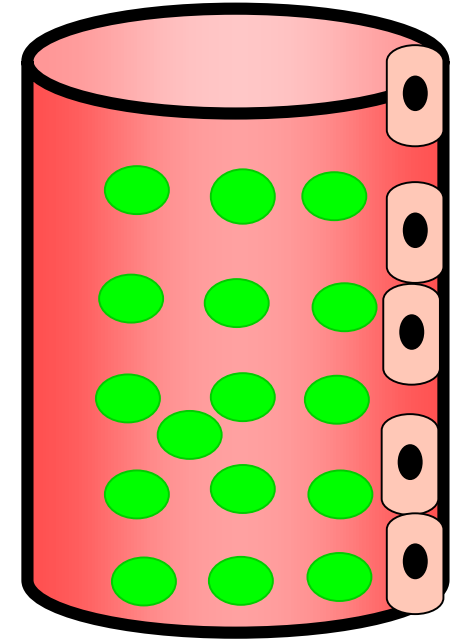
- ❑ Time required by the body to decrease plasma concentration of a drug by 50%
- ❑ It depends upon kinetics of drug elimination (clearance) e.g. metabolism and excretion and volume of distribution (V_d).

Drug concentration in Plasma

Decline by one half



Time



Pharmacokinetic Parameters

Plasma half life ($t_{1/2}$)

□ For some drugs, their **Biological $t_{1/2}$ > Plasma $t_{1/2}$**

e.g. **Reserpine** :Irreversible ↓ of vesicular enzymes (**Hit & Run**). Its effect does not depend on its presence in plasma & ends by resynthesis of new vesicles.

□ * Repeated administration of a drug at regular intervals (first order kinetics) will reach a **plateau plasma concentration (Steady State Concentration “C_{ss}”)** within **4-5 $t_{1/2}$** .

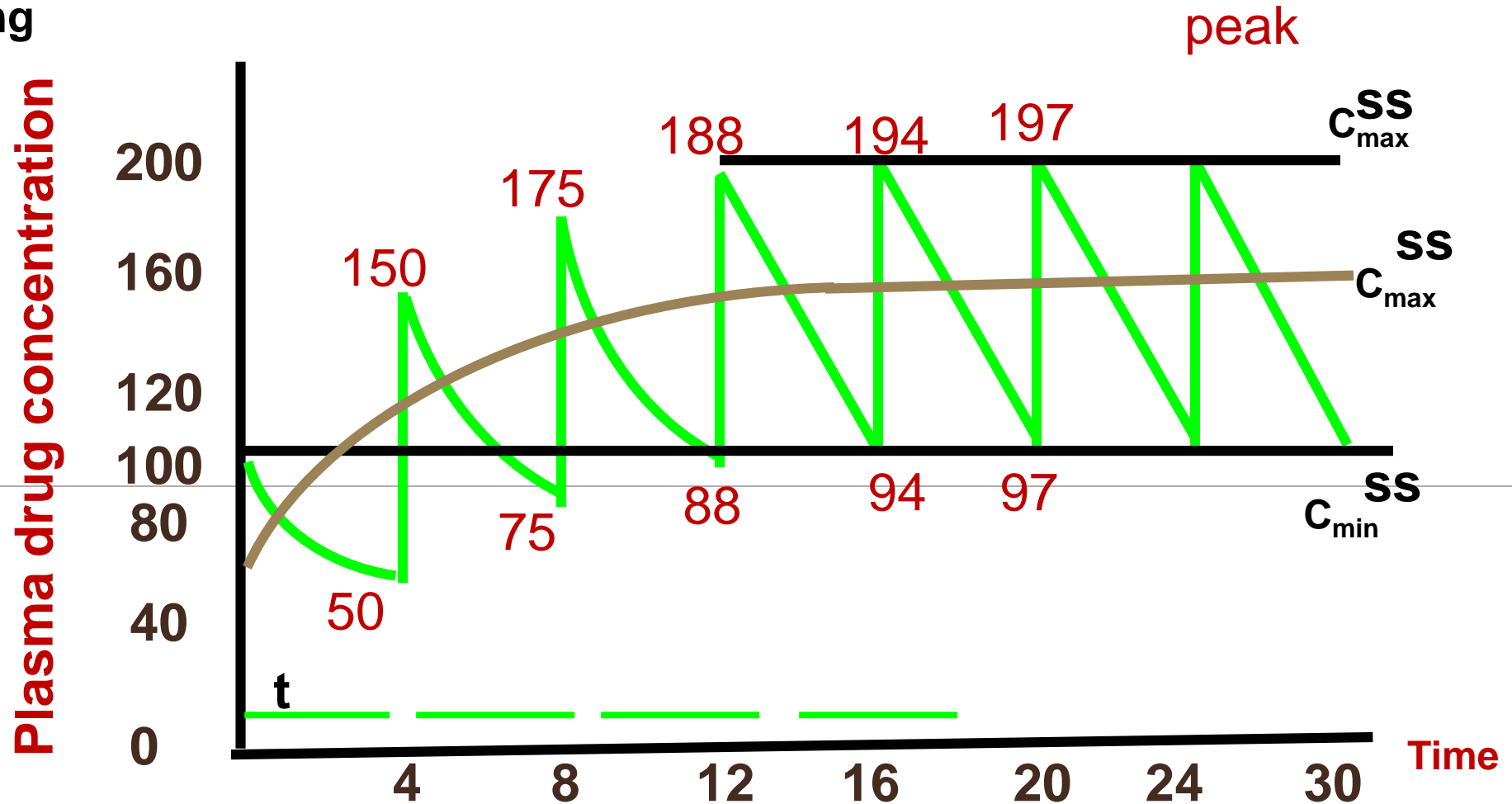
□ *Most of the drug (**> 95%**) **disappears** from the body **within 4-5 $t_{1/2}$ after stopping its intake.**

□ $t_{1/2}$ is useful to determine **the frequency & route of drug administration.**

Steady state concentration: (C_{ss})

This concentration is attained after 4-5 half lives, when a drug is administered repeatedly at a constant rate.

Dose = 100 mg



$t_{1/2} = 4$ hours

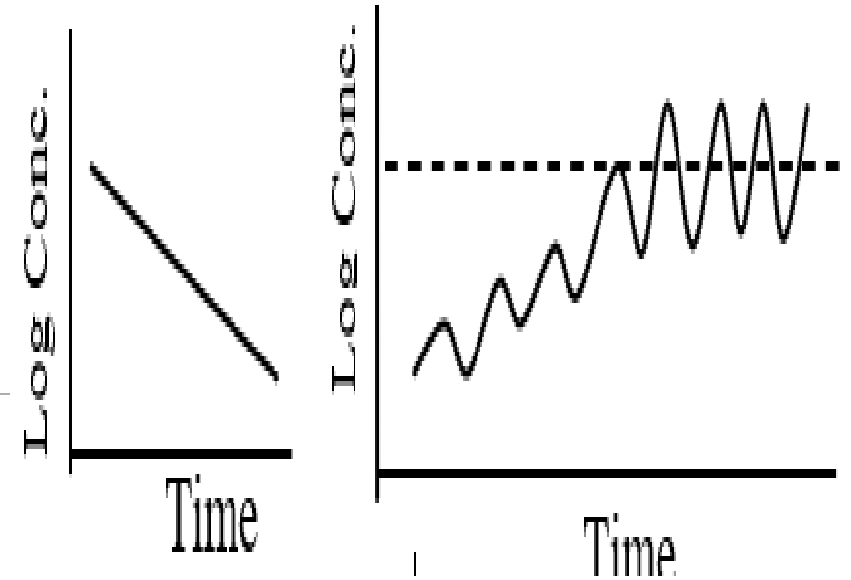
Fundamental Principles of Pharmacokinetics

- Elimination processes may be **first or zero order kinetics**.



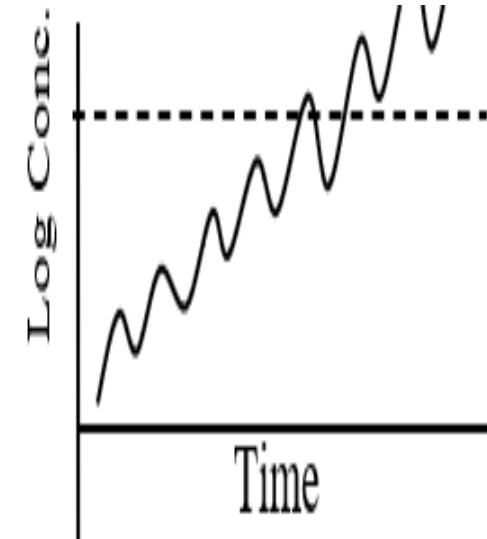
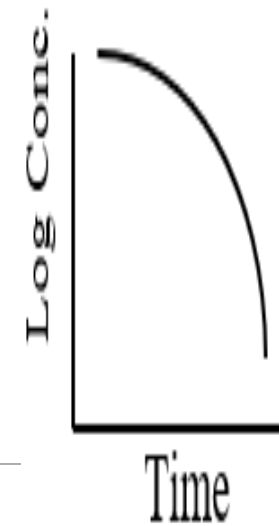
First order kinetics:

- 1- Kinetics of drug (ADME) **are PROPORTIONAL to its concentration.**
- 2- **Fixed FRACTION (%) of the drug is eliminated per unit time.**
- 3- **LINEAR** drug disappearance curve.
- 4- **CONSTANT $t_{1/2}$.**
- 5- **AUC is PROPORTIONAL to drug concentration.**
- 6- Repeated intake of the drug at regular intervals
---- **Css within 4 – 5 $t_{1/2}$.**
- 7- Examples:
 - **Most drugs obey first order kinetics.**
 - **S.D. of most of drugs** such as Aspirin, Phenytoin



Zero order(Saturation) kinetics:

- 1- Limited capacity of drug's kinetics due to **SATURATION** of involved enzyme &or carrier = Rate of kinetics is Fixed and NOT proportional to drug concentration.
- 2- **Fixed AMOUNT** of the drug is eliminated per unit time.
- 3- **NON-LINEAR** drug disappearance curve.
- 4- **t_{1/2}** increases with drug conc.
- 5- **AUC** is NOT proportional to drug concentration.
- 6- If rate of intake of drug > Rate of its elimination ----
Cumulation ---↑ C_{ss} ----Toxicity.
- 7- **Examples:** **L.D. of most of drugs** such as Aspirin, Phenytoin.

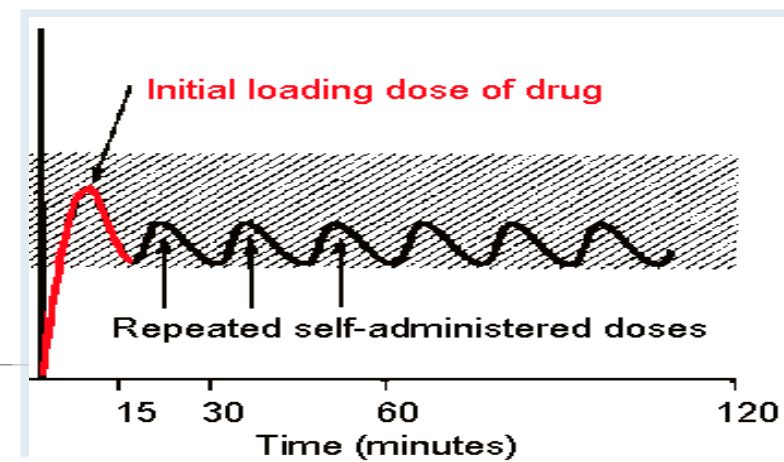


DOSAGE OF DRUGS (POSODOLOGY)



Dosing
terminology

Loading dose



- The initial dose of the drug which can **raise its plasma level to the target concentration.**
- Used to **reach C_{ss} very rapidly as in emergency** e.g. digoxin in acute heart failure.
- **Loading dose = $V_d \times$ desired concentration (C_{ss}).**
- **Unexpected toxicity** can occur

Maintenance dose

□ The dose needed to **replace the drugs eliminated** since the preceding dose, **so maintain steady state (C_{ss})**.

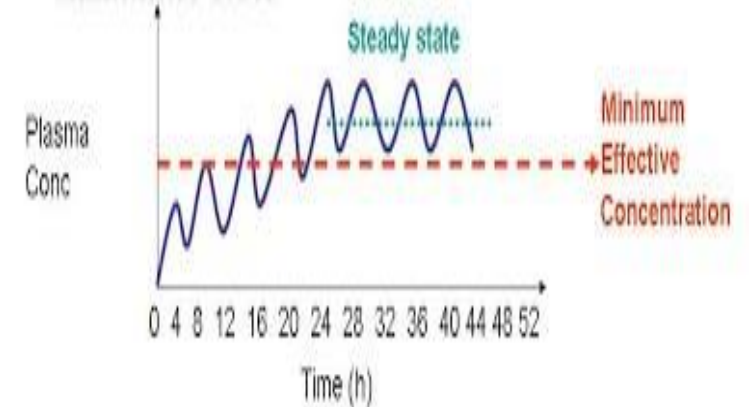
□ **The maintenance dose = $Cl \times C_{ss} \times T_m$**

Cl = Clearance

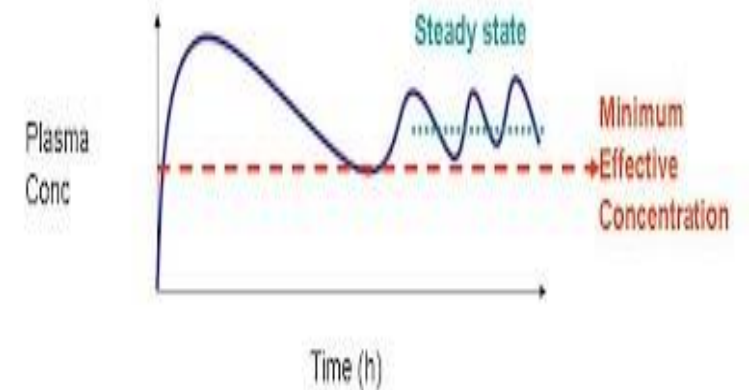
C_{ss} = steady state concentration

T_m = dose interval

• Maintenance doses



• Loading dose and Maintenance doses



Lethal dose:

The dose that produces **death** in **all** exposed animals (**fatal dose**).

LD50 (median lethal dose):

Minimum dose that produces death in **50%** of experimental animals.

ED50 (median effective dose):

The dose that produces a certain pharmacological effect in 50% of experimental animals.

*Therapeutic index: LD50 / ED50

It is measure for **safety** of drugs.

The **higher** the index, the **safer** the drug.

Therapeutic window



It is the range between minimum effective dose and minimum toxic dose .

Some drugs have narrow therapeutic window as phenytoin and theophylline.

What to do to prevent their toxicity ????



Questions

- 1. What is the significance of therapeutic window ???*
- 2. Define loading dose and its significance.*





Thank You

