
Clinical pharmacokinetic and
therapeutic drug monitoring

Definitions

- **Pharmacokinetic:** is the study of the time course of absorption, distribution, metabolism and excretion (ADME) of drugs in the body.

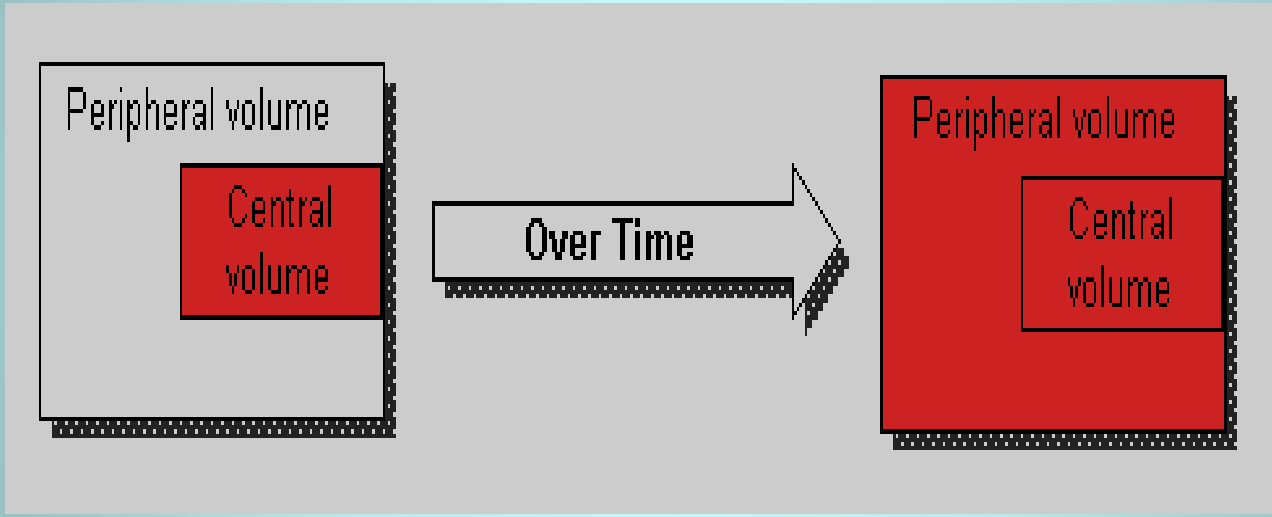
- **Clinical Pharmacokinetic :**deals with the application of Pharmacokinetic principles in the drug therapy to ensure safe and effective therapeutic management.

- **Absorption:** When drugs are given extravascularly (e.g., orally, intramuscularly, applied to the skin via a transdermal patch, etc.), *absorption* must take place for the drug molecules to reach the systemic circulation.

- **Distribution:** occurs when drug molecules that have entered the vascular system pass from the bloodstream into various tissues and organs such as the muscle or heart.

All drugs initially distribute into an initial compartment (blood and tissues which are highly perfused by blood) before distribution into the peripheral compartment.

As shown in the following figure:



If the distribution is completed quickly → the drug is said to follow one –compartment model.

If the distribution is completed slowly → the drug is said to follow two –compartment model.

- **Metabolism:** is the chemical conversion of the drug molecule, usually by an enzymatically mediated reaction, into another chemical entity referred to as a *metabolite.*

- **Excretion:** is the irreversible removal of drug from the body and commonly occurs via the kidney or biliary tract.

- **Therapeutic Drug monitoring :** is the measurement of the serum level of the drug ands the coordination of this serum level with the therapeutic range .

Goals of TDM:

1. Assess medication compliance
2. Avoid toxicity
3. Increase therapeutic response

❖ **There are a number of criteria which should be fulfilled before TDM is considered :**

1-the drug has narrow therapeutic index
2-Significant consequences from toxicity.
3-There is a large variability in pharmacokinetic parameters values among patients.
4-ready available assay method.

In the absence of these criteria , the only indication for TDM is to monitor compliance or to confirm toxicity.

Sources of Errors in TDM

Common potential sources of error are:

1. Administration times not recorded accurately.
2. Dose administration error.
3. Blood drawn at incorrect time.
4. Blood drawn before steady-state.
5. Blood drawn from wrong site.
6. Lab assay error.
7. Pharmacy dispensing error.

Drug commonly monitored in hospitals

A-Antibiotics : Aminoglycosides , Vancomycin.

B-Cardiovascular Agents: Digoxin, Lidocaine, Procainamide, Quinidine.

C-Anticonvulsants: Phenytoin, Carbamazepine, Valproic Acid, Phenobarbital, Primidone.

D- Immunosuppressant : Cyclosporine, Tacrolimus.

E- Other Drugs: Lithium. Theophylline

Pharmacodynamics : refers to the relationship between drug concentration at the site of action and the resulting effect, including the time course and intensity of therapeutic and adverse effects. The effect of a drug present at the site of action is determined by that drug's binding with a receptor.

- Receptors may be present on:-

- neurons in the central nervous system to depress pain sensation,
- cardiac muscle to affect the intensity of contraction,
- or even within bacteria to disrupt maintenance of the bacterial cell wall.

For most drugs, the concentration at the site of the receptor determines the intensity of a drug's effect

Basic pharmacokinetic concepts

- **Volume of distribution (Vd) :the apparent volume into which a drug distributes in the body at equilibrium.**

- **Vd = Amount of drug in the body**
  Plasma drug concentration

Vd may be used to calculate the loading dose (LD) required to achieve the desired plasma conc. (Cp).

$$\mathbf{LD} = \frac{Vd.Cp}{F}$$

f=is the bioavailability of the drug.

e.g.: calculate the loading dose of drug (X) required to achieve a conc. of 20 mg/L to a patient with body Wt of 70 kg knowing that the Vd =0.7 L/kg

Sol.

$$LD = \frac{Vd.Cp}{F}$$

$$= \frac{0.7 * 70 * 20}{1}$$

$$= 980 \text{ mg}$$

Q:- JM is a 50 y.o ,70 Kg , male , has bacterial pneumonia. his GP decide to give him (X) antibiotic intraveneously and the minimum antibiotic plasma conc. Which inhibit bacterial growth is 20 mg/l, the Vd is 0.7 l/kg, what should be the dose??

❖ **Clearance (Cl):-** ability of organs of elimination to clear drug from the blood stream .

Or can be defined as :- vol. of blood in a defined region of the body that's cleared of drug in a unit time.

Units are in L/hr

Mathematically, Cl is the product of of the first orderelimination rate constant(ke) and the apparent Vd

Cl=Ke.Vd

Ke is the fraction of the amount of drug in the body eliminated per time

➢ The Ke is used to predict how Cp varies with time

$Cp_2=Cp_{1*}\ e^{-ke\ t}$

❖ **Clearance (cl) determines the maintenance dose (MD) required to obtain a given steady-state serum conc.(Css):**

$$MD = Css * Cl$$

in the case of steady state :- the amount of drug administered is equal to the amount of drug eliminated within one dosing interval

Q:-TJ is a 67-year-old, 70-kg male being treated for chronic obstructive pulmonary disease.Sustained-release oral theophylline is being added to his drug regimen. Assuming V = 40 L, and Cl = 20ml/min, compute an oral theophylline maintenance dose to be administered every 12 hours that would achieve a Css = 8 mg/L.

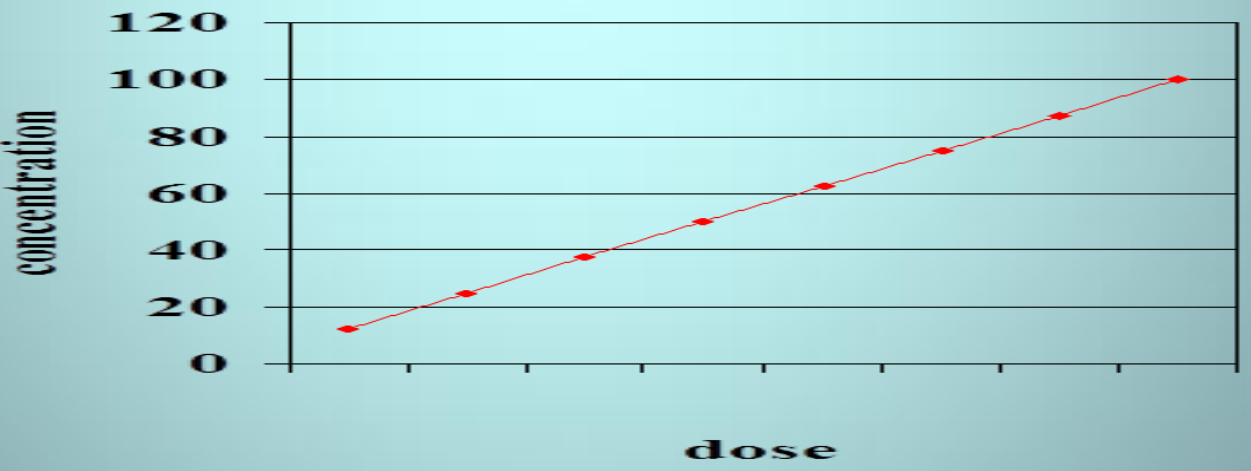
❖ **Half-life ($t_{1/2}$):-** the time required to reduce the plasma conc.to one half its initial values

$$T_{1/2} = \frac{0.693}{Ke} \quad \text{or} \quad T_{1/2} = \frac{0.693 * Vd}{Cl}$$

Q:-LM is a 59-year-old, 85-kg male needing treatment with oral quinidine for an arrhythmia. Assuming F = 0.7, Ke=0.087/h, compute $T_{1/2}$ for a dose of oral quinidine 400 mg every 6 hours.

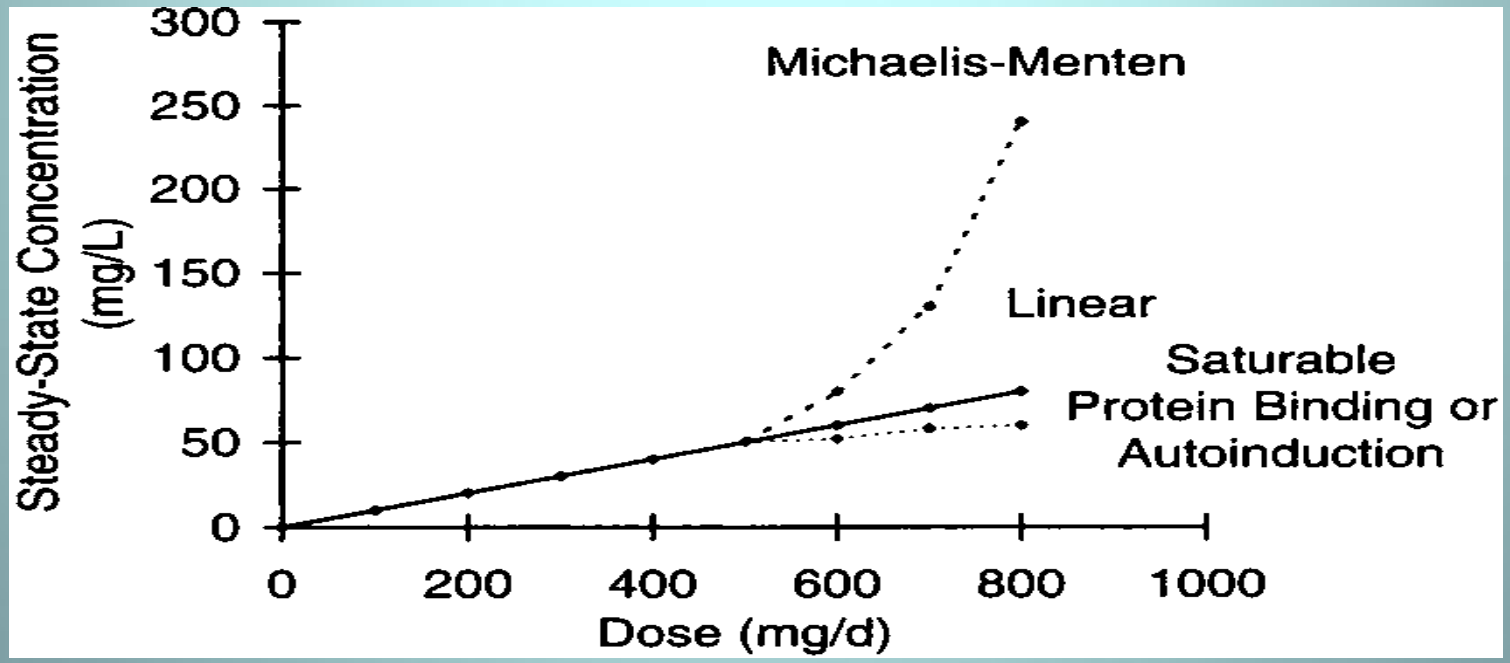
Linear Pharmacokinetics

- Linear = rate of elimination is proportional to amount of drug present
- Dosage increases result in proportional increase in plasma drug levels



Nonlinear Pharmacokinetics

- Nonlinear = rate of elimination is constant regardless of amount of drug present
- Dosage increases saturate binding sites and result in non- proportional increase/decrease in drug levels



MICHAELIS-MENTEN OR SATURABLE PHARMACOKINETICS

- Drugs that are metabolized by the cytochrome P-450 enzymes and other enzyme systems may undergo Michaelis-Menten or saturable pharmacokinetics. This is the type of nonlinear pharmacokinetics that occurs when the number of drug molecules overwhelms or saturates the enzyme's ability to metabolize the drug. When this occurs, steady-state drug serum concentrations increase in a disproportionate manner after a dosage increase. Under steady-state conditions the rate of drug administration equals the rate of drug removal.

Therefore,for a drug that is solely removed by metabolism via one enzyme system, the Michaelis-Menten equation can be used to compute the maintenance dose (MD) required to achieve a target steady-state serum concentration (Css):

$$MD = \frac{Vmax * Css}{Km + Css}$$

where **Vmax** is the maximum rate of metabolism, **C** is the substrate concentration,
and **Km** is the substrate concentration where the rate of metabolism = Vmax/2