⇒ Pharmacology → Study of exogenously administered Chemical molecules with living systems

⇒ Pharmacodynamic → physiological & Biochemical effect of drugs and their mechanism of action at molecular / subcellular / organ level

⇒ Pharmacokinetics → movement of the drug inside the living system & its alteration by the living system.
e.g. absorption, distribution, Metabolism & Excretion

⇒ Pharmacotherapeutics → use of pharmacological Knowledge for the prevention & cure of the disease

⇒ Clinical pharmacology → scientific study of drugs in humans. i.e healthy volunteers & patients for pharmacokinetics & pharmacodynamic Investigation.

⇒ Pharmacy → It is the art & science of Compounding drugs or preparing suitable dosage forms for administration of drugs.

⇒ Toxicology → It is the study of poisonous effect of drugs & other chemicals.

Drug Nomenclature

(a) Chemical name → N-(4-Hydroxyphenyl) acetamide

(b) Non proprietary name → Paracetamol

(c) Proprietary name → Dolo or

Essential drug Concept → Those that satisfy the priority healthcare need of population

Orphan drugs →

⇒ Route of drug administration :— Appropriate Route is decided based on the drug as well as patient related factors

⇒ factors governing the choice of route →

(1) Physical & chemical properties of drugs - eg: solid, liquid, gas, solubility, stability, pH & irritancy.

(2) site of desired action → localized & approachable & Generalized & non approachable

(3) Rate & Extent of absorption of drug from different route

(4) Effect of digestive Juice & first pass metabolism of drug

(5) Rapidity with which the response is desired.

(6) Accuracy of dosage required (Inhalation & I.V. can provide fine tuning)

(7) Condition of the patient (unconcious & comating)

Routes decided in two parts — < Local route / systemic route

(1) Local route → TOPICAL < skin / mucous membrane
→ deeper tissue
→ ~~Infusion~~ ~~membrane~~
→ Arterial Supply

Skin → drug is applied as ointment, cream, paste powder, dressing & spray

mucous membrane → mouth & pharynx, eyes, conjunctiva Gastrointestinal tract, Bronchi & lungs, urethra, vagina & Anus (anal)

Deeper tissue → certain deep area can be approached by using a syringe and needle

Arterial supply → close intra-arterial injection is used for contrast media in angiography.

Systemic routes → drug is intended to be absorbed in blood & distributed all over the body, including the site of action.

(1) Oral (2) Sublingual or buccal
(3) Rectal (4) Cutaneous (5) Inhalation
(6) Nasal (7) Parentral (8)

Oral → Oldest & most common mode of drug administration.

advantage

(1) safer & convenient
(2) does not need Assistance
(3) Non invasive,
(4) painless
(5) medicine need not to be sterilized

limitation

(1) Action is slower not suitable for emergency
(2) unpalatable drugs are difficult
(3) may causes nausea & vomitting.
(4) can not be used for

(5) Not suitable for poorly absorb drugs

(6) Not suitable for drug which are destroyed by digestive Juice.

Sublingual ⇒ only lipid soluble & non irritant drugs can be administered

⇒ action is fast

⇒ By pass the liver - hence first pass metabolism can be avoided

Rectal ⇒ Less preferred, however certain irritant & unpleasant drug can be applied as suppositories

Cutanious ⇒ Highly lipid soluble drugs can be applied over the skin for slow & prolonged absorption.

*Transdermal therapeutic system ⇒ drug is held in a ~~coiter~~ reservior between a occulsive backing film & rate controlling microfore membrane.

→ drug is ~~delivered~~ delivered at ~~skin~~ skin surface by diffusion for percutanious absorption.

→ Contain adhesive layer with priming dose.

Inhalation → Volatile liquid & gases are given by inhalation
→ Absorption takes place from the vast surface of Alveoli – action is very rapid.

Nasal → The mucous membrane of the nose can readily absorb many drugs, digestive juice and liver can are bypassed.

Parentral ⇒ administration of drug through the injection which takes the drug directly into the tissue fluid or blood without having to cross the intestinal mucosa

Subcutaneous → drug is deposited in the loose subcutaneous tissue which is richly supplied by nerves,
→ irritant drugs can not be injected
→ Less vascularized.
eg. Jermoject
Pellet implantation
Biodegradable implants.

Intramuscular (I.m.) → The drug is injected in one of the large skeletal muscle
→ less richly supplied with nerves.
→ mild irritant drugs can be injected.

Intravenous → Drug is injected as bolous or slowly into the blood stream
→ Highly irritant drugs can be injected.
→ Rapid action

Pharmacokinetics

P'Kinetics → Quantitative Study of drug movement in, through & out of the body

→ intensity of Response is related to the concentration.

→ Transport of drug across the biological membrane.

Biological membrane ⇒ This is a bilayer (100 A° thick)

→ made up of phospholipid & cholesterol molecules

→ polar groups are oriented at the two surfaces whereas non polar groups are embeded in the matrix.

Drugs are transported across the membrane by

(a) Passive diffusion & filteration.

(b) Specilized transport.

(a) Passive diffusion → Drug is diffuses across the membrane in the direction of its concentration gradient

→ membrane play no active role in this process

→ Rate of transport is proportional to lipid-water partition coefficient

Influence of pH ⇒ most drugs are weak electrolyte i.e. their ionization is pH dependent (strong electrolytes - nearly completely ionised at acidic as well as basic pH).

Ionization of weak acid or weak base is given by Henderson-Hasselbalch equation

for a weak acid $HA \rightleftharpoons H^+ + A^-$

$$pH = pK_a + \log [A^-]/[HA]$$

or $$\log [A^-]/[HA] = pH - pK_a$$

Thus pKa is equal to pH at which the drug is 50% ionized

- Implication of this → weak acidic drugs are unionized at gastric pH & thus absorb from stomach
  - → weak base drugs are unionized at intestinal pH & thus absorb from intestine.
  - → Acidic drugs are ionized more in alkaline urine & thus do not back diffuse in kidney tubules
  - → Basic drug are excreted faster in acidified urine

Ion trapping → unionized form of a acidic drug which cross the surface membrane of gastric mucosal cells, reverts to the ionized form with in the cell (pH 7.0) and then only slowely passes to the extracellular fluid this is called to ion trapping.

filteration → Filteration is the passage of drug through aqueous pores in the membrane or through paracellular spaces. This can be accelerated if hydrodynamic flow of the solvent is occuring under hydrostatic or osmotic pressure gradient

- → majority of cells have very small pores (4 A°)

and drug with MW > 100 or 200 dalton are not able to penetrate.

- → However capillaries (except in brain) have

Specialised transport ⇒ Two types < Carrier mediated
Pinocytosis

Carrier mediated transport < Active transport
Facilitated diffusion

↳ Drug combines with a carrier present in the membrane and the complex then translocate from one face of the membrane to another face

* Active transport → movement occurs against the concentration gradient, needs energy & is inhibited by metabolic poisons

⇒ It results in selective accumulation of drugs on the one side of the membrane

* facilitated diffusion ⇒ This proceeds more rapidly than simple diffusion and translocate even non diffusable substances

→ Does not require energy

Pinocytosis ⇒ It is the process of transport across the cell in particulate form by formation of vesicles

→ Proteins and other big molecules are transported.

ABSorption

→ movement of drug from its site of ~~absorption~~ administration to into circulation.

→ Both Rate & Extent of drug absorption are important

→ Absorption can be controlled by many

factors affecting drug absorption ⇒

Aqueous solubility → For poorly water soluble drugs rate of dissolution governs the rate of absorption
→ Solution form of a drug is absorbed faster the solid form of same drug.

Concentration ⇒ Passive transport depend on the concentration gradient
→ Drug given as concentrated solution is absorbed faster then from dilute solution.

Area of absorbing surface ⇒ Larger is the area of absorbing surface faster is the absorption

Vascularity of the absorbing surface → Blood circulation removes the drug from site of absorption and maintain concentration gradient

Route of administration → Each Route has its own peculiarities hence affect the drug absorption

Oral Route ⇒ The effective barrier for the drugs is the epithelial lining of gastrointestinal tract which lipoidal.
→ Non ionized lipid soluble drugs are readily absorb from stomach as well as intestine e.g. Ethanol
→ acidic drugs are absorb from stomach while basic drugs absorb from intestine (Duodenum)
→ However for acidic even for acidic drugs absorption from stomach is slower because the mucosa is thick

→ Particle size in the solid dosage form governs the Rate of dissolution and in turn of absorption

→ Presence of food ~~Reduces~~ dilute the drug and retards absorption

→ Certain drugs form complexes with food constituents e.g. tetracycline with ~~food~~ ~~Constituents~~. calcium present in milk.

→ most drugs are absorbed better if taken in empty stomach

→ Highly ionized drugs, e.g. Streptomycin, neostigmine are poorly ~~absorb~~ absorbed when given orally

→ Absorption of a drugs can be affected by other concurrently ingested drugs
e.g. antacids & phenytoin with Sucralfate
Tetracycline with iron preparations

→ Alteration of gut flora by antibiotics may disrupt the enterohepatic cycling of oral contraceptive & digoxin

Subcutaneous & intramuscular route → By this route drug is directly deposited in the ~~vessels~~ vicinity of the ~~capillaries~~ capillaries.

→ very larger molecules are absorbed through lymphatics.

→ ~~S.C. site~~ Subcutaneous site is slower than Intra-muscular.

→ Both S.C. & I.M. are faster and more consistent

Topical route ⇒ Systemic absorption after topical application depends primarily on lipid solubility of drugs

→ few drugs significantly penetrate intact skin
eg Clonidine, Nitroglycerine

Bioavailability

→ Rate & Extent of drug absorption from a dosage form
→ It is a measure of fraction of administered drug that reaches the systemic circulation in the unchanged form
→ Bioavailability of a drug can be less due to
(a) Incomplete absorption (b) Absorbed drug may undergo first pass metabolism

→ Incomplete bioavailability after S.C. or I.M. injection is less common but may occure due to local binding of drug.

Bioequivalent ⇒ Two preparations of drug are considered bioequivalent when ~~some manufacturers may observe~~ Rate & Extent of bioavailability of the drug from them is not significantly different under suitable conditions.

→ Tablets & Capsules contains a number of other materials - diluent, stabilizing agents, binders, lubricants etc. The nature of these as well as details of the manufacturing such as force used in compressing the table may affect its disintegration.
→ Differences in bioavailability are seen mostly with Poorly soluble and slowly absorbed drugs.
→ Reduction in particle size increases the rate

Distribution

→ Once a drug has gained access to blood stream, it gets distributed to other tissues that initially had no drug

→ Concentration gradient being in the direction of plasma to tissue

→ The extent of distribution of a drug depends on its lipid solubility, ionization at physiological pH, extent of binding to plasma and tissue proteins & differences in regional blood flow.

→ movement of drug proceed until an equilibrium is established between unbound drug in plasma & tissue fluid.

Apparent volume of distribution (V) → Presuming that the body behave as single homogenous compartment with volume V into which drug gets immediately and uniformly distributed.

$$V = \frac{\text{dose administered I.V.}}{\text{plasma Concentration.}}$$

Thus 'V' defined as "the volume that would accomodate all the drug in the body" if the concentration throughout was same as in plasma.

factors governing volume of drug distribution

→ Lipid: water partion coefficient
→ pKa value of the drug
→ Degree of plasma protein Binding

→ disease like CHF, uremia & cirrhosis.

Redistribution ⇒ Highly lipid soluble drugs given I.V. or by inhalation initially get distributed to organs with high blood flow, eg: brain, heart, kidney etc.

→ Later less vascular but more bulkey tissues (muscles, fat) takeover the drug -

→ Greater the lipid solubility of drug faster is the redistribution.

→ eg: Anaesthetic action of thiopentone is terminated in few minutes due to redistribution.

Penetration into brain & CSF ⇒ The capillary endothelial cells in the brain have tight junctions & lack longer intercellular spaces. further Glial cells cover the capallaries & collectively known as blood brain barrier.

→ only lipid soluble drugs are able to penetrate BBB

→ Efflux carries like P-glycoprotein present in brain capalaries extrude many drugs that enter by other processes.

→ There is also an enzymatic blood brain barrier. monoamine oxidase, Choline estrase and some other enzymes present in the capalliary walls or in the cells lining not allows catechodamines, 5HT, Acetylcholine to ~~active~~ enter in brain in its active form.

Passage across placenta ⇒ placental membrane. also allows lipophilic drugs while restrict hydrophilic drugs.

→ Incomplete barrier & most of the drug are

Plasma protein binding ⇒ most drugs posses affinity for plasma proteins. Acidic drugs generally bind to ~~glycoproteins~~ plasma proteins & basic drugs to α_1-acid glycoproteins.

→ Binding to albumin is quantitatively more important
→ Extent of binding depends on individual compound
→ Highly plasma protein bound drugs are largely restricted to the vascular compartment and tend to have lower volume of distribution.
→ The bound fraction is not available for action however it is in equilibrium with free drug in plasma & dissociate when concentration of free drug falls due to elimination

⇒ e.g. drugs bounds to Albumin
— Warfarin, Benzodiazepine & Barbiturates

With α_1 acid glycoprotein
β-blockers, Lignocaine, Quinidine

→ High degree of plasma protein Binding generally makes a drug longer acting.
→ Plasma Concentration of drug refers to bound as well as free drug.
→ One drug can bind to many sites on the albumin Conversely, more than one drug can bind to same site
→ eg. Indomethacin displace warfarin.

Tissue storage ⇒ Drugs may also accumulates in specific organs or get bound to specific tissue constituents

eg Iodine bind to thyroid

Thiopentone → to adipose tissue

Metabolism

metabolism or Biotransformation means chemical alteration of the drug in the body

→ A process that convert non polar compound to polar so that they can easily excreated.

→ most hydrophilic drugs eg streptomycin, neostigmine are not biotransfored & excreated unchanged in urine

→ metabolism is a process that has developed to protect the body from ingested toxins

→ The primary site for drug metabolism is liver others are kidney, intestine, lungs, plasma

→ Biotransformation of drug may lead to the following.

① Inactivation ② Active metabolite from active drug

③ Activation of inactive drug

Inactivation

active drug is converted into inactive form

eg. Pentobarbital.

Active metabolite from active drug

Codeine

(i) Inactivation → most drugs & their active metabolites are render inactive or less active eg: Pentobarbitone, morphine, propranolol

(ii) Active metabolite from active drug ⇒
many drugs have been found to be partially converted to one or more active metabolite from active drug
→ effect is sum total of parent drug & its active metabolites.

(iii) Activation of inactive drug ⇒ Few drugs are inactive as such and need conversion in the body to one or more active metabolites.
eg Levodopa → Dopamine

Biotransformation reactions are classified into
- phase I or Non synthetic
- phase II or synthetic or Conjugation

Phase I Biotransformation
- oxidation
- Reduction
- Hydrolysis
- Cyclization
- Decyclization.

is oxidation
→ This reaction involves addition of oxygen or negatively charged radicals or removal of hydrogen or positively charged radicals.

→ most important drug metabolizing reactions
eg: Hydroxylation, oxygenation, at C, N or S atom

oxidation reactions are mostly carried by a group of monooxygenase in the liver, which in the final step involves a cytochrome P450 - haemoprotein

Reduction ⇒ converse of oxidation & involves cyt P450 enzyme working in opposite direction
eg: Chloramphenicol & Halothane

Hydrolysis ⇒ cleavage of drug molecules by taking up a molecule of water.

Ester + H_2O $\xrightarrow[\text{esterase}]{}$ Acid + Alcohol

Cyclization ⇒ formation of ring structure from Straight chain compound.
eg progesamid

Decyclization → opening of Ring structure of a cyclic molecule
eg Barbiturates
minor pathway.

Synthetic reaction

① Glucuronide conjugation
② ~~Sulfation~~ Acetylation.
③ methylation.

⑤ Glycine Conjugation
⑥ Glutathion conjugation
⑦ Ribonuclease side & Ribonucleotide synthesis

Synthetic or phase II - Biotransformation reactions: ⇒

- Involve conjugation of drug or its phase I metabolite with an endogenious substrate, generally derived from carbohydrate or amino acids to form a polar highly ionized organic acid, which is easily excreted in urine or bile.

→ Conjugation reactions have high energy requirement

(I) Glucuronide Conjugation ⇒ This is the most important synthetic reaction

→ Compounds with a hydroxyl or carboxylic acid group are easily conjugated with Glucuronic acid which is derived from Glucose

e.g ASpirin, Phenacetin, morphine

→ Not only drugs but endogenious substrates like bilirubin, steroidal hormones and thyroxine utilize this pathway.

→ Drug glucuronides excreted in bile can be hydrolysed by bacteria in the gut → the librated drug is reabsorbed and undego same fate.

→ Entrohepatic cycling of the drugs prolong its ~~fate~~ action.

⇒ e.g Phenolphthalein, oral Contraceptives.

(II) Acetylation ⇒ Compounds having amino or hydrazine residue are conjugated with the help of acetyl Co-enzyme A

e.g: Sulfonamides (Drugs)

multiple genes control the acetyl transferases and rate of acetylation shows genetic polymorphism
i.e slow & fast acetylators.
Isoniazid ; Sulphonamides.

(III) methylation ⇒ The amines and phenols can be methylated, methionine & cysteine acting as a methyl donors. e.g. Adrenaline, histamine, nicotinic acid

(IV) Sulphate Conjugation ⇒ The phenolic ~~and~~ compounds and steroids are sulphated by sulphokinases
e.g. chloramphenicol, Adrenal, sex steroid.

(V) Glycine Conjugation ⇒ Drugs having Carboxylic acid groups are conjugated with glycine, but this is not a major pathway of metabolism
e.g. salicylates

(VI) Glutathione Conjugation ⇒ It serve to inactivates highly reactive quinones or epoxides intermediates formed during metabolism of certain drugs e.g. Paracetamol.

Drug → Quinones & Epoxides → Glutathione Conjugation → Mercapturates → Excreted

(VII) Ribonucleoside/Nucleotide synthesis ⇒ It is important for the activation of many purines & Pyrimidine antimetabolites used in cancer chemotherapy.

Drug metabolizing enzymes → microsomal
→ Non microsomal

Microsomal ⇒ These enzymes are located on smooth endoplasmic reticulum (a system of microtubule inside the cell)
Primarily in liver, also in kidney, intestinal mucosa and lungs.

→ They catalyze most of the oxidation, reduction, hydrolysis & Glucuronide conjugation.

→ microsomal enzymes are inducible by drugs, diet, and other agencies.

Non microsomal enzymes ⇒ These are present in the cytoplasm and mitochondria of hepatic cells as well as in the other tissues including plasma.

→ flavo-protein oxidases, esterases, amidases and conjugases are some non microsomal enzymes

Reactions catalyzed are - oxidation, reduction
hydrolytic reactions.
Conjugation except - Glucuronide Conjugation

→ Non microsomal enzymes are not inducible but many shows genetic polymorphism
(eg: acetyltransferases & pseudocholine esterases)

→ amount & kind of drug metabolizing enzymes is controlled genetically & also altered by ~~factors~~ environmental factors

⇒ Thus marked interspecies & inter individual differences are seen

e.g. Cats are deficient in glucuronyl transferase

Dogs are deficient in Acetyl transferase

→ upto 6 fold differences in the rate of metabolism of a drug among normal human adults may be observed.

Hofmann ~~elimn~~ elimination ⇒ This refers to true inactivation of the drug in the body fluids by spontaneous molecular rearrangement without any enzyme

eg. Atracurium.

Inhibition of drug metabolism ⇒ One drug may competitively inhibit the metabolism of another drug if it utilizes the same enzymes as cofactor

→ However such interactions are not common as ~~one would expect~~

→ most of the drugs at therapeutic concentrations are metabolized by non saturation kinetics i.e. the enzyme present in excess.

→ Enzyme inhibition is a faster process as compared to enzyme induction.

→ metabolism of drugs with high hepatic ~~concentration~~ Extraction ratio depend on liver blood flow.

Excretion

→ Excretion is the passage out of systamically absorbed drug

→ Drug & their metabolites are excreted in:-

1. Urine
2. faeces
3. Exhaled air
4. Saliva & sweat
5. milk

① Urine → Through the kidney it is the most Important channel of excretion for most of the drugs

② faeces :→ Apart from the unabsorbed fraction, most of the drug present in faeces is derived from bile.

→ Relatively large molecules are preferentially eleminated in the bile

③ Exhaled air → Gases & volatile liquids are eliminated by lungs, irrespective of their lipid solubility

→ Alveolar transfer of the gas/vapour depends on its partial pressure in the blood.

→ Lungs also serve to trap and extrude any particulate matter injected I.V.

e.g. General Anaesthetics, Alcohol

④ Saliva & sweat ⇒ These are of minor importance for drug excretion.

Milk → The excretion of drug in milk is not important for ~~drug~~ ~~excretion~~ mother but the suckling infants inadvertently receive the drug.

→ most drug enter milk by passive diffusion.

Renal Excretion → Kidney is Responsible for excretion of all water soluble substances

→ The amount of ~~water~~ drug or its metabolite present in urine is the sum total of glomerular filteration, tubular reabsorption & tubular secretion

Glomerular filteration →

→ Glomerular Capalaries have larger Pores

→ All non protein bound drug presented to the glomerulus is filtered.

→ Glomerular filtration depends on plasma protein binding & blood flow.

→ GFR decline after the age of 50 and is low in renal ~~fail~~ faiure

Tubular reabsorption → depends on lipid Solubility & ionization of the drug at existing urinary pH

→ 99% of Glomerular filterate is reabsorbed

→ lipid soluble drugs filtered at the glomerulus back diffuses in the tubules.

→ Non lipid soluble & highly ionized drugs are unable to ~~reb~~ reabsorbed.

→ Rate of excretion of such drugs are proportional to GFR

→ Changes in urinary pH affect tubular reabsorption of drugs that are partially ionized.

→ This principle is utilized for facilitating elimination of drugs in poisoning, i.e. urine is alkalinized in barbiturates ~~poi~~ while acidified in morphine poisoning.

→ Effect of change in pH is more on the drug with pKa between 5 to 8

Tubular secretion ⇒ This is the active transfer of organic acids & bases by two separate & non specific mechanism which operates in the proximal tubules

→ GFR ↔ 120 ml/min, if renal clearance of a drug is more than GFR suggest existance of tubular process.

→ Efflux transporters - P-glycoproteins / MRP2 are located in luminal membrane

eg: organic acid transport → uric acid, probenecid

organic base transport → quinine cimetidine.

→ Tubular transport is bidirectional

→ For drugs & their metabolite, secretion into the tubular lumen is predominate whereas on endogenious substance like uric acid is predominantely reabsorbed!

→ Drug utilizing the same transport compete with each other.

eg: Quinidine decreases the renal & biliary clearance of digoxin

→ Due to underveloped tubular transport action of many drugs is longer in neonates.

Kinetics of elemination

Clearance (CL) → is the theoritical volume of plasma from which the drug is completely removed in unit time.

$$\text{Clearance (CL)} = \frac{\text{Rate of Elimination}}{\text{Concentration}}$$

Clearance can follows -

First order (exponential) kinetics → The Rate of elimination is directly proportional to drug concentration

CL → remains constant

Zero order kinetics → Rate of elimination remain constant irrespective of drug concentration

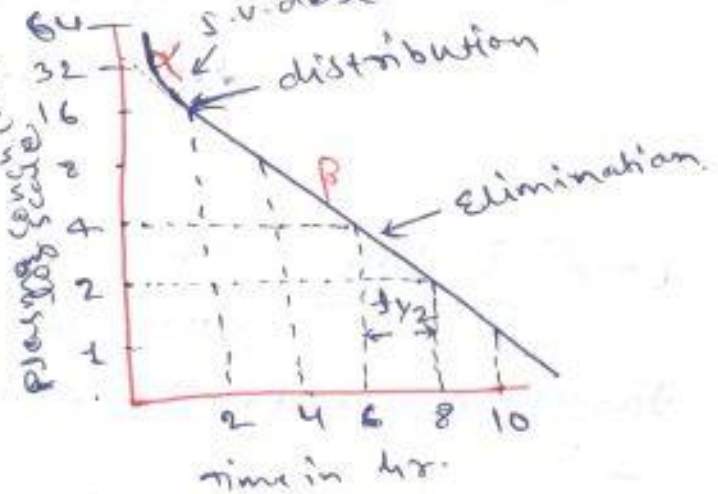
CL - decreases with increase in concentration.

Plasma half life → Time taken for its plasma level to half of its original

→ If a drug has one compartment of distribution & first order elimination when given by I.V. a semilog plasma concentration time plot as shown in fig. is obtained

The plot has two slopes

→ Initial rapid decline (α) phase – due to distribution
→ less declined β phase due to elemination



→ At least two half lifes i.e. distribution half life & elimination half life can be calculated.

⇒ The elimination half life is simply called as "half life" of drug

mathematically,

elimination $t_{1/2}$ is $t_{1/2} = \frac{\ln 2}{K}$

where ln2 is $\log_2(0.693)$

K → elimination Rate Constant of drug.

$$K = \frac{\text{Clearance (CL)}}{V}$$

therefore $$t_{1/2} = 0.693 \times \frac{V}{CL}$$

→ For first order kinetics → $t_{1/2}$ remains constant because V and CL do not change with dose

→ zero order kinetics → $t_{1/2}$ increases with dose because CL progressively decreases as dose is increased

Steady state plasma concentration (C_{pss}) → when a drug repeated at relatively short interrals, it accumulates in the [illegible] balance input and a steady

$$C_{pss} = \frac{\text{dose rate}}{CL}$$

→ If C_L is known then dose rate needed to achieve the target C_{pss} can be determined -

$$\text{dose rate} = \text{target } C_{pss} \times C_L$$

After oral administration only a fraction of (F) of the dose reaches systemic circulation in the active form

$$\text{dose rate} = \text{target } C_{pss} \times \frac{C_L}{F}$$

Loading dose → This is single of few quickly repeated doses given in the beginning to attain target concentration rapidly, it may be calculated as -

$$\text{Loading dose} = \frac{\text{target } C_p \times V}{F}$$

Thus loading dose is governed by V and not by CL or $t_{1/2}$

maintainance dose → This dose is one that is to be repeated at specific intervals after the attainment of target C_{pss} so as to maintain same by balancing elemination

maintenance dose

$$\text{dose rate} = \frac{\text{target } C_{pss} \times CL}{F}$$

governed by CL or $t_{1/2}$ of the drug.

monitoring of plasma concentration of drug → C_{pss} of a drug attain in a given patient depends upon its F, V and CL in that patient. Because each of

⇒ measurment of plasma drug concentration can give an estimate of the pharmacokinetic variables in that patient and the magnitude of deviation from the average patient.

⇒ Revised dose can be calculated for such patients

~~Revised~~ If drug is obeying first order kinetics

$$\text{Revised dose} = \frac{\text{previous dose rate} \times \text{Target } C_{ss}}{\text{measured } C_{ss}}$$

⇒ Therapeutic drug monitoring is particularly useful in the following situation:-

(I) Drug with low safety margin – digoxin
(II) if individual variations are large
(III) Potentially toxic drugs are used in the presence of Renal failure
(IV) In case of poisoning
(V) In case of failure of response without any apparent reason.
(VI) To check Patient Compliance

Monitoring of plasma concentration is of no value ⇒

(I) drug whose Response is easily measurable. → general anesthetic
(II) Drugs activated in the body → Levodopa
(III) Hit & run drugs → i.e. ~~drug~~ whose effect lasts much longer than the drug itself → Reserpine.
(IV) drugs with irreversible action – eg. ~~organo~~ Organophosphate & anticholinesterases.

Prolongation of drug action. ⇒ It is sometime advantagious to modify a drug such that it acts for a longer period of time. by doing so

(i) frequency of administration reduced.
(ii) Improved patient Compliance
(iii) Large fluctuation in plasma Concentration are avoided
(iv) Drug effect could be maintain overnight without disturbing sleep.

→ drug with $t_{1/2}$ less than 4hr are suitable for Controlled release formulations.
→ while no need for drugs with $t_{1/2}$ more than 12 hr.

Action can be prolonged by →

(1) Prolonging absorption from site of administration
- → oral → Coated with Resins
- → Parenteral → As oily Solution, ~~bio~~ biodegradable implants.
- → Transdermal → drugs implanted as adhesive patches, strips

(2) By increasing plasma protein binding.
→ Congeners have been prepared which are highly bound to plasma proteins and are slowly released.

(3) By retarding rate of metabolism → small chemical modification may markedly affect the rate of metabolism without affecting the biological action.

(4) By retarding renal excretion. → By