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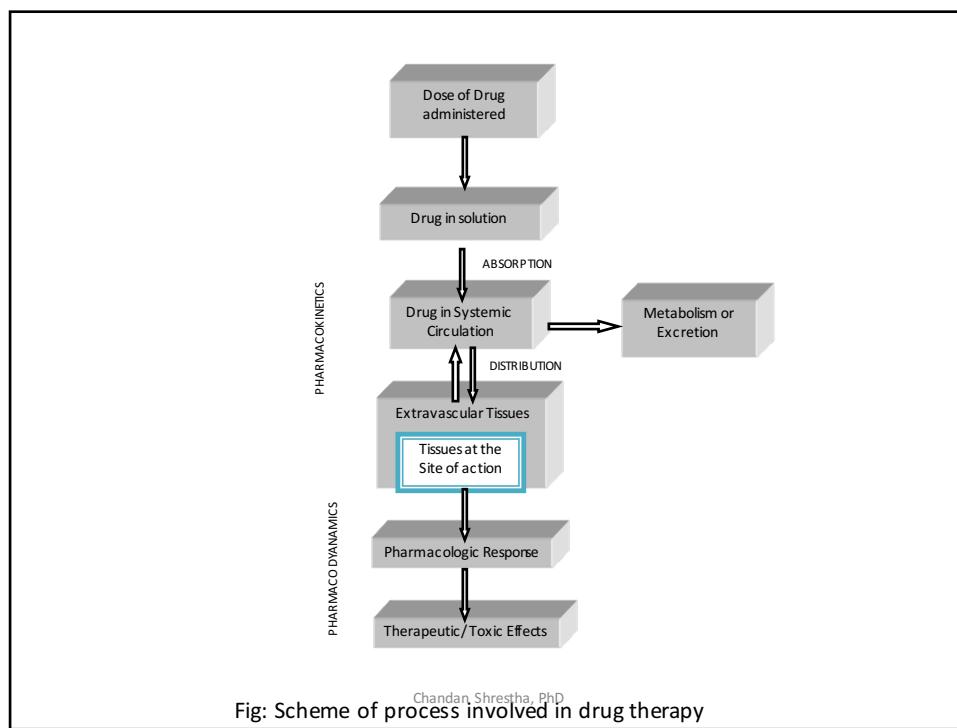


Fig: Scheme of process involved in drug therapy

Pharmacokinetic ParametersPeak Plasma Concentration (C_{max})Time of Peak Concentration (t_{max})

Area under the Curve (AUC)

Pharmacodynamic Parameters

Onset of Action

Onset Time

Duration of Action

Intensity of Action

Minimum Effective Concentration (MEC) / Antibiotics (MIC)

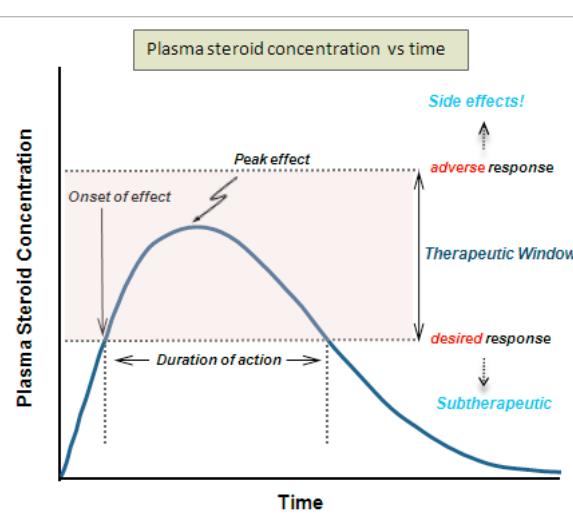
Maximum Safe Concentration (MSC)

Therapeutic window (TDM)

Therapeutic ratio

Half-life ($t_{1/2}$)**Bioavailability****Bioequivalent****Steady state****Loading Dose**

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Maintenance dose

Peak Plasma Concentration (C_{max})

- Also known as Peak height concentration or maximum drug concentration.
- The point of maximum concentration of drug in plasma is called peak and the concentration of drug at peak is known as peak plasma concentration.
- Unit: mcg/mL.

Time of Peak Concentration (t_{max})

- The time for drug to reach peak concentration in plasma.
- Unit: hours

Area under the Curve (AUC)

- Represents the total integrated area under the plasma level-time profile.
- Total amount of drug that comes into the systemic circulation after its administration.
- Unit: mcg/mL × hours.

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Onset of Action

- It is the beginning of pharmacologic response.
- Occurs when the plasma drug concⁿ just exceeds the required MEC.

Onset Time

- It is the time required for a drug to start producing pharmacologic response.
- Corresponds to the time for the plasma concⁿ to reach MEC after administration of drug.

Duration of Action

- It is the time period for which the plasma conc^c of drug remains above MEC level.

Intensity of Action:

- Also called peak response.
- It is the maximum pharmacologic response produced by the peak plasma concⁿ of drug.

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Minimum Effective Concentration (MEC)

- MEC defined as minimum concentration of drug in plasma required to produce the therapeutic effect.
- Concⁿ of drug below MEC is said to be in the *sub therapeutic level*.
- In case of Antibiotics, it refers as Minimum Inhibitory Concentration.
(Describes the minimum concentration of antibiotic in plasma required to kill or inhibit the growth of microorganisms)

Maximum Safe Concentration (MSC)

- Also called minimum toxic concⁿ (MTC).
- It is the concⁿ of drug in plasma above which adverse or unwanted effects are precipitated.
- Concⁿ of drug above MSC is said to be in the *toxic level*.

Therapeutic Range / Therapeutic window

- It is the drug concⁿ between MEC and MSC.
- Refers to either the dosage range or blood plasma or serum concentration usually expected to achieve desired therapeutic effects.

Bioavailability is defined as the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action. Bioavailability of parenteral route is 100%. Simply, it is percentage, amount or concentration of drugs that reaches to systemic circulation and becomes available at the site of action.

Types: Absolute bioavailability and relative bioavailability

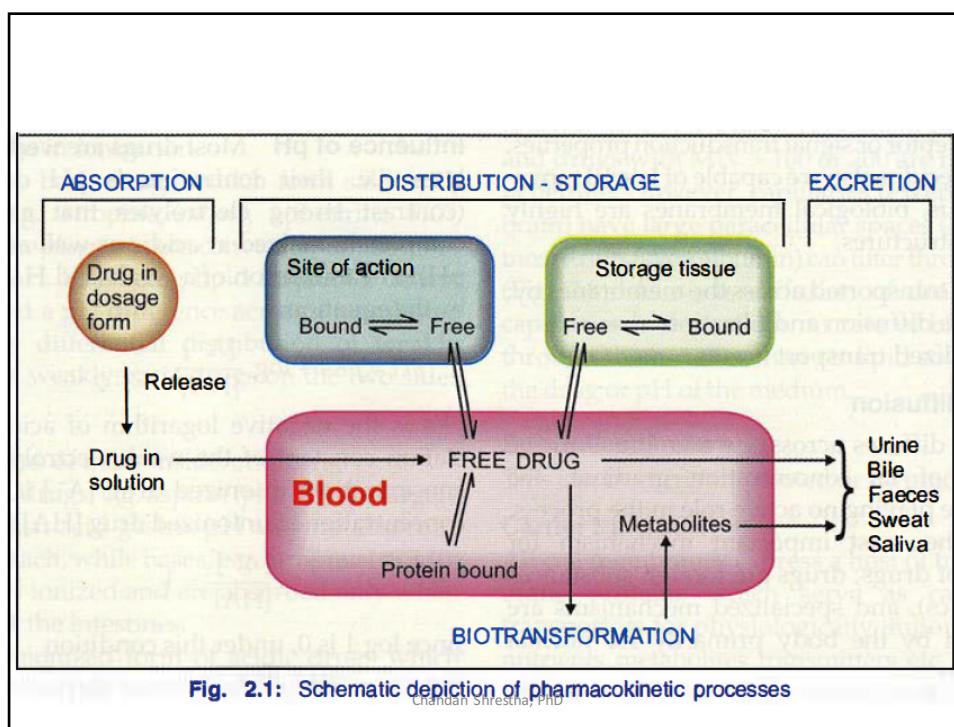
Self: Factors affecting bioavailability

Bioequivalence is defined as the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study.

Pharmacokinetics

- The study of what the body does to the drug.
- The quantitative study of drug movement in, through and out of the body.
- Involves four process:
 - ❖ **Absorption:** *movement of drug from its site of administration into the circulation.*
 - ❖ **Distribution:** *Drug molecules from BLOOD to TISSUES.*
 - ❖ **Metabolism / Biotransformation:** *Chemical alteration of drug in the body.*
 - ❖ **Excretion:** *Elimination of drugs or its chemical by process.*

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Absorption

- The process of movement of unchanged drug from the site of administration to systemic circulation.
- Drugs exert their Pharmacological actions only when they come into blood circulation from their site of application and for this absorption is an important step.
- Completely but poorly absorbed drug may fail to show therapeutic response as the plasma concentration for desired effect is never achieved.
- On the contrary, a rapidly absorbed drug attains the therapeutic level easily to elicit pharmacological effect, thus both the rate and the extent of drug absorption are important.

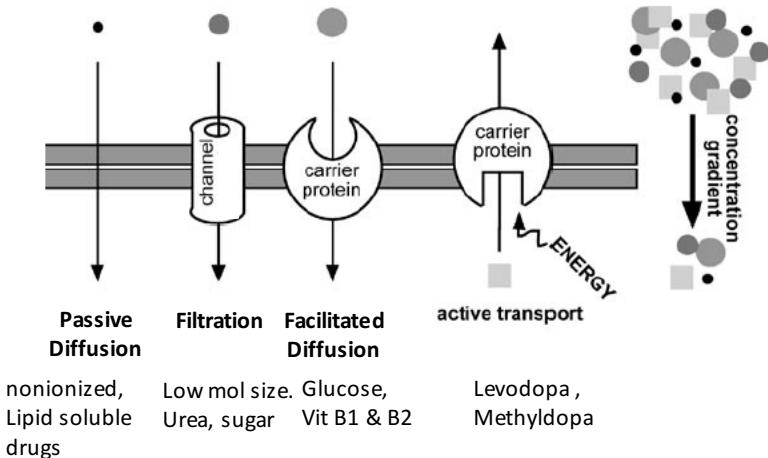
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Mechanism of drug absorption

- Passive diffusion
- Pore transport/ Filtration
- Carrier mediated transport
 - ❖ Facilitates diffusion
 - ❖ Active transport
- Endocytosis
 - ❖ Phagocytosis
 - ❖ Pinocytosis

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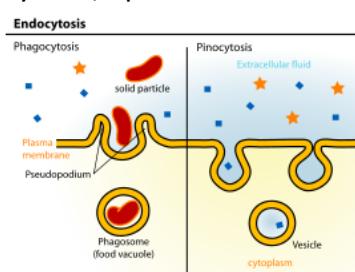
Mechanism of drug absorption



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Endocytosis:

- This includes 2 types of processes:
 - ✧ Phagocytosis; adsorptive uptake of solid particulates &
 - ✧ Pinocytosis; uptake of fluid



- cellular uptake of macromolecular nutrient like fat, starch vit A, D, E, K & insulin.

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Factors affecting drug absorption

- Aqueous Solubility
- Concentration
- Area of absorbing surface
- Vascularity of the absorbing surface
- Route of Administration

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Aqueous Solubility

- Solid dosage form (tab, cap) should dissolve first before absorption.
- For Poor water soluble drugs (aspirin, griseofulvin), rate of dissolution governs rate of absorption.
- Drug in solution absorbed faster than drug in solid form.

Concentration

- Higher the concentration greater the rate of absorption.

Area of absorbing surfaces

Larger the surface area, faster is the absorption

Vascularity of the absorbing surface

Higher the blood flow, greater the absorption because increased blood flow removes the drug from the site of absorption and maintains concentration gradients.

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Oral Route

➤ Food in stomach: retards the absorption.

May forms complex. Tetracycline and milk

➤ Gastric pH: Basic drug but not acidic drug are largely ionized by acidic pH in stomach.

Rate of absorption, unionized > anionic > cationic

Unionized drug poorly absorbed from the stomach because of mucosa is thick, covered with mucus and the surface area is small.

➤ Gastric juice: may degrade drugs. Penicillin G, insulin and are ineffective orally. (Enteric coated tablets)

➤ Drug interactions: may form insoluble complex (phenytoin with sucralfate)

➤ Gastric emptying: faster the gastric emptying accelerates the absorption.

High fat meal slow the gastric motility, reduces absorption.

Subcutaneous and intramuscular

Large lipid insoluble drug may be absorbed.

Rate of absorption, im>sc; but faster than oral route.

Application of heat and muscular exercise accelerates drug absorption by increasing blood flow.

Topical Sites

Systemic absorption depends upon the lipid solubility.

Few drugs significantly penetrate intact skin (nitroglycerin, estradiol).

Absorption can be promoted by rubbing the drug by the use of occlusive dressing.

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Distribution

Involves the transport of pharmacologic agents throughout the body.

Factor determining distribution of drugs

- Blood flow to body tissue
- Lipid solubility
- Affinity to different tissue
- Drug-protein complexes
- Drug-Drug interaction
- Physical Barrier

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Blood flow to body tissue

- High blood supply in Heart, brain, liver, kidney
- Low in skin, bone, adipose tissue.

Lipid solubility: quickly absorption thus rapid distribution

Affinity to different tissue

- Bone marrow, teeth, eyes and adipose tissue have high affinity for certain drugs.
- Thiopental, diazepam and lipid soluble in Adipose tissue
- Tetracycline binds to calcium and accumulates in bone and teeth.
- Once stored in tissue, remain in body for many month and released very slowly back to the circulation.

Drugs concentrated in tissues

<i>Skeletal muscle, heart</i>	— digoxin, emetine (bound to muscle proteins).
<i>Liver</i>	— chloroquine, tetracyclines, emetine, digoxin.
<i>Kidney</i>	— digoxin, chloroquine, emetine.
<i>Thyroid</i>	— iodine.
<i>Brain</i>	— chlorpromazine, acetazolamide, isoniazid.
<i>Retina</i>	— chloroquine (bound to nucleoproteins).
<i>Iris</i>	— ephedrine, atropine (bound to melanin).
<i>Bone and teeth</i>	— tetracyclines, heavy metals (bound to mucopolysaccharides of connective tissue), bisphosphonates (bound to hydroxyapatite)
<i>Adipose tissue</i>	— thiopentone, ether, minocycline, phenoxybenzamine, DDT dissolve in neutral fat due to high lipid-solubility; remain stored due to poor blood supply of fat.

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Drug-protein complexes

- Acidic drugs binds to plasma albumin and basic drugs to α_1 acid glycoprotein.
- These complexes are too large to cross capillary membranes thus not available for distribution.
- Warfarin 99% bound to plasma protein and is unavailable to reach target cells.

Drugs highly bound to plasma protein

<i>To albumin</i>	<i>To α_1-acid glycoprotein</i>
Barbiturates	β -blockers
Benzodiazepines	Bupivacaine
NSAIDs	Lidocaine
Valproic acid	Disopyramide
Phenytoin	Imipramine
Penicillins	Methadone
Sulfonamides	Prazosin
Tetracyclines	Quinidine
Tolbutamide	Verapamil
Warfarin	

Drug Drug interaction

- Aspirin displace Warfarin from drug protein complex, thus raising blood levels of free warfarin and dramatically enhances the risk of hemorrhage.

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Physical Barrier.*Blood brain barrier:*

- ✓ High lipid soluble drugs penetrate BBB
- ✓ sedatives, antianxiety and anticonvulsants readily cross BBB to produce their action on CNS.
- ✓ In contrast antitumor drug do not easily cross this barrier making brain cancer difficult to treat.
- ✓ Inflammation (bacterial meningitis or encephalitis) may increase the permeability, permitting the passage of ionized lipid-insoluble compounds (e.g., penicillin and ampicillin).

Fetal placental barrier:

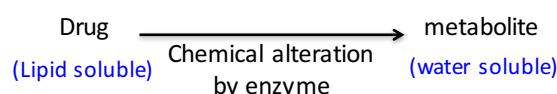
- protective function
- Prevents potentially harmful substances from passing from mother's bloodstream to the fetus.
- Alcohol, cocaine, caffeine easily cross this barrier and can potential harm the fetus

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Metabolism/ Biotransformation

Drug metabolism is the chemical alteration of a drug in the body by enzyme.

Metabolism is defined as the process of conversion from one chemical form to another chemical form by the help of enzymes.



By product of metabolism is known as metabolite. Metabolites are more polar than parent compound.

Metabolism normally results in pharmacologic inactivation of drugs. Hence metabolites have little or no pharmacologic activity.

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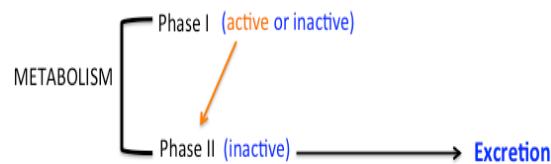
Metabolism/ Biotransformation

- Primary site of metabolism: **LIVER.** (Cytochrome P-450)
- Others- Kidney, Intestine, lungs and plasma

Biotransformation reaction can be classified into:

Phase I- includes Oxidation, Reduction, Hydrolysis etc. mostly mediated by CYP450 enzymes to form more polar molecule

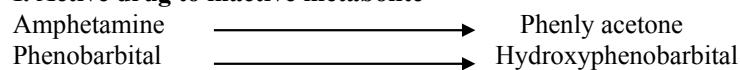
Phase II- conjugation of drugs or its phase I metabolite with substances such as glucuronic acid, glutathione, sulfate, acetic acid etc to form polar, highly ionized organic acid, which is easily excreted in urine or bile



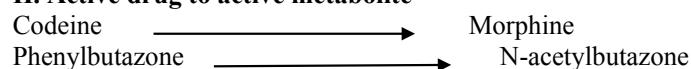
Metabolism/ Biotransformation

Biotransformation of drugs may lead to the following.

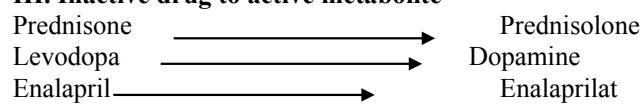
I. Active drug to inactive metabolite



II. Active drug to active metabolite



III. Inactive drug to active metabolite



<i>Active drug</i>	<i>Active metabolite</i>	<i>Prodrug</i>	<i>Active form</i>
Chloral hydrate	— Trichloroethanol	Levodopa	— Dopamine
Morphine	— Morphine-6-glucuronide	Enalapril	— Enalaprilat
Cefotaxime	— Desacetyl cefotaxime	α -Methyldopa	— α -methylnorepinephrine
Allopurinol	— Alloxanthine	Dipivefrine	— Epinephrine
Procainamide	— N-acetyl procainamide	Sulindac	— Sulfide metabolite
Primidone	— Phenobarbitone, phenylethylmalonamide	Proguanil	— Cycloguanil
Diazepam	— Desmethyl-diazepam, oxazepam	Prednisone	— Prednisolone
Digitoxin	— Digoxin	Bacampicillin	— Ampicillin
Imipramine	— Desipramine	Sulfasalazine	— 5-Aminosalicylic acid
Amitriptyline	— Nortriptyline	Cyclophosphamide	— Aldophosphamide, phosphoramide mustard, acrolein
Codeine	— Morphine	Fluorouracil	— Fluorouridine monophosphate
Spironolactone	— Canrenone	Mercaptoperine	— Methylmercaptopurine ribonucleotide
Losartan	— E 3174	Acyclovir	— Acyclovir triphosphate

A prodrug is a medication that is administered in an inactive or less than fully active form, and is then converted to its active form through a normal metabolic process

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Factors affecting Drug metabolism

Age

- Hepatic enzyme activity is generally reduced in pediatric and geriatric patients, therefore more sensitive to drug.

Disease condition

- Severe liver disease (cirrhosis)..... Reduced metabolic activity.....reduction in dose.

Genetic disorder

- lack specific metabolic enzymes

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Factors affecting Drug metabolism

Drug interaction

Enzyme Induction: Few drugs have ability to increase metabolic activity in liver.

Examples-

- Anticonvulsants including phenobarbitone, rifampin, glucocorticoids induce CYP3A isoenzymes.
- Isoniazid and chronic alcohol consumption induce CYP2E1.
- Other important enzyme inducers are: chloral hydrate, griseofulvin, DDT.

Enzyme Inhibition

- Drugs inhibit the metabolic activity in liver.
- Leads to toxicity of the drugs.
- Ciprofloxacin, itraconazole, ketoconazole, omeprazole etc...

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Drugs that inhibit drug metabolizing enzymes	
Allopurinol	Diltiazem
Omeprazole	Amiodarone
Erythromycin	Propoxyphene
Clarithromycin	Isoniazid
Chloramphenicol	Cimetidine
Ketoconazole	Quimidine
Itraconazole	Disulfiram
Metronidazole	Verapamil
Ciprofloxacin	MAO inhibitors
Sulfonamides	Ritonavir (and other
Fluoxetine (and other SSRIs)	HIV protease inhibitors)

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Excretion

- Removal of drug from the body.
- Urine, Faeces, saliva and sweat, exhaled air, milk.
- The rate at which drugs are excreted determines the conc of the drug in the blood stream and targets.
- Concentration of drugs in the bloodstream determines their duration of action.
- Primary site: kidney
- Others: lungs, bile, skin

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Factors affecting drug excretion

- Kidney Impairment
- Concentration of drug
- Blood Flow
- Degree of ionization
- Lipid solubility
- Drug protein complexes
- pH

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Factors affecting drug excretion

Kidney Impairment

- Reduced ability to excrete drugs and may retain drugs for an extended time or may increase the conc of drug.
- Dose must be reduced.

Concentration of drug

- Glomerular filtration and tubular reabsorption are passive process.

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Factors affecting drug excretion

Degree of ionization

- Ionized drug are not reabsorbed and thus excreted.

Lipid solubility

- Are reabsorbed from the tubule and then circulate back to the blood

Drug protein complexes

- Too large; Not filtered at the glomerulus
- Sometimes secreted into the distal tubule.
- 10 % penicillin G is filtered at the glomerulus; 90% secreted in renal tubule.

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Factors affecting drug excretion

pH

- Excretion may be fast if the pH of filtrate changes.
- Weekly acidic drug (aspirin) in alkaline filtrate.....ionized...remain in the filtrate and be excreted in the urine.
- Weekly Basic Drug (diazepam) ionized in acidic filtrate.
- Advantages of pH and drug excretion----- critical care situation
- Aspirin overdose patient..... Sodium bicarbonate
- Diazepam-----ammonium chloride

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Kinetics of elimination

Zero order kinetics

- "Elimination of a constant quantity per time of the drug quantity present in the organism."
- Rate of elimination is independent to concentration of drug.
- For example 2 mg are eliminated every hour.
- Ethanol, Phenytoin, Theophyline, warfarin

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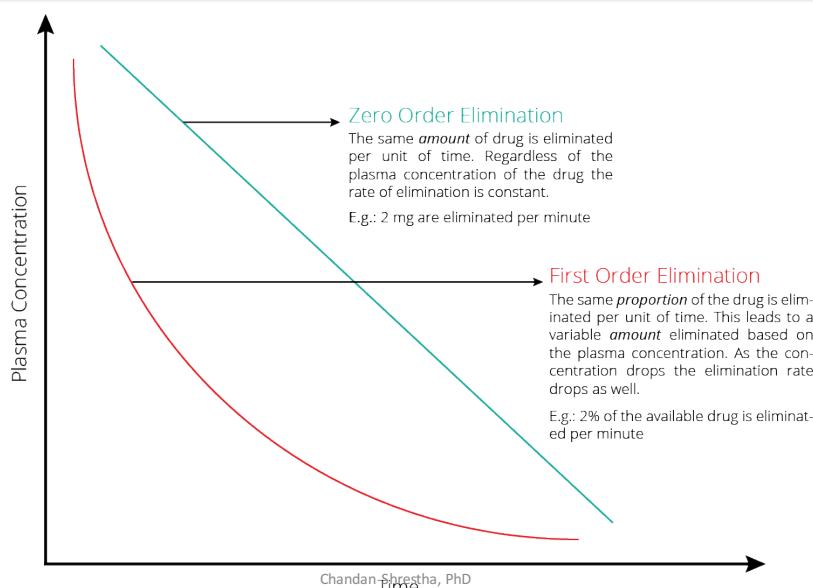
Kinetics of elimination

First Order kinetics

- "Elimination of a constant fraction per time unit of the drug quantity present in the organism. The elimination is proportional to the drug concentration."
- Rate of elimination is dependent to the drug concentration.
- For example, 2% of the drug quantity is eliminated per minute.
- Many drugs are eliminated by first order kinetics.

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Kinetics of elimination



Plasma half lives and steady state concentration

Plasma Half Life ($t_{1/2}$)

Time taken for its plasma concentration of drug to be reduced half of its original value.

Unit: h

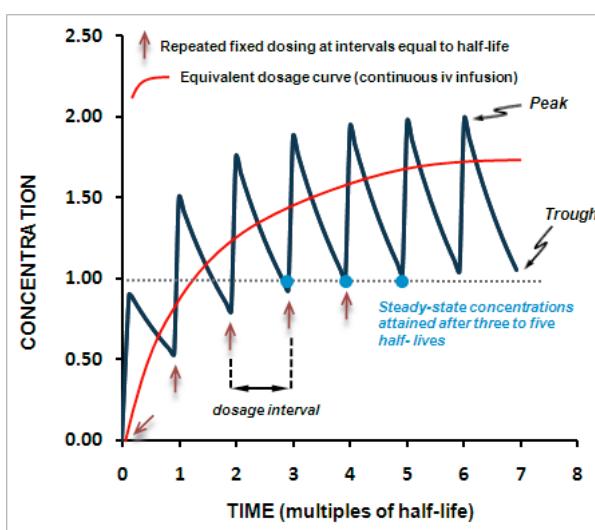
Complete drug elimination occurs in 4-5 half lives.

Steady State Concentration

Refers to a situation where Rate of drug input is equal to rate of drug elimination

In practice, it is generally considered that steady state is reached when a time of 4 to 5 times the half-life for a drug after regular dosing is started

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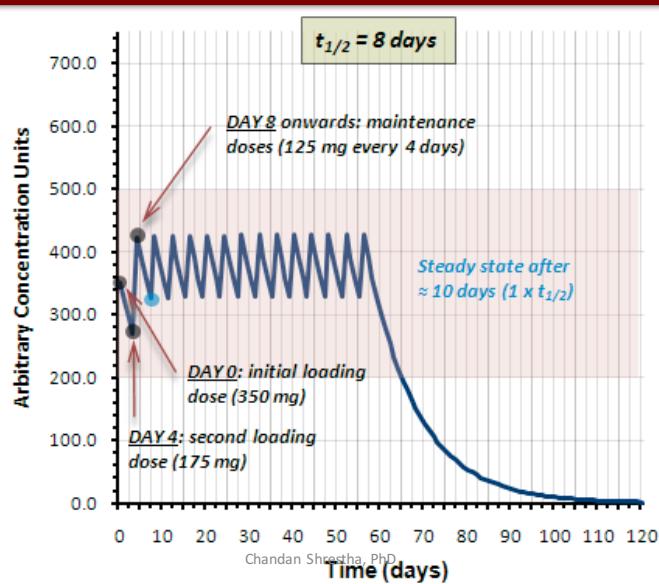
Loading dose and Maintenance dose

Loading Dose is higher amount of drug given in the beginning to attain the target concentration rapidly.

Maintenance Dose is the dose of drug given at a regular dosing interval to achieve the plasma drug concentration in the therapeutic range.

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Loading dose and Maintenance dose



Therapeutic Drug Monitoring

TDM is the measurement of specific drugs at intervals in order to maintain a relatively constant concentration of the medication in the bloodstream.

TDM is useful in the following situations:

- *Drugs with low safety margin or narrow therapeutic ratio:* Digoxin, theophylline, anticonvulsants, antiarrhythmics
- *Potentially toxic drugs used in the presence of renal failure-* aminoglycosides antibiotics
- *If individual variations are large-* antidepressants
- *In case of poisoning*
- *In case of failure of response without any apparent reason-* antimicrobials
- *To check patient compliance-* psychopharmacological agents.

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Drugs requiring TDM

- Drug acting on CVS- Digoxin, Amiodarone
- Antibiotics- aminoglycosides
- Antiepileptics- phenobarbitone, phenytoin, valproic acid, carbamazepine, gabapentine
- Psychopharmacological agents- lithium, amitriptyline, nortriptyline, clozapine
- Immunosuppressants- cyclosporine, tacrolimus
- Antiinfective- cycloserine, ethambutol, pyrazinamide, streptomycin

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Monitoring of plasma concentration is of no value

1. Drugs whose response is easily measurable antihypertensives, hypoglycaemics, diuretics, oral anticoagulants, general anaesthetics.
2. Drugs activated in the body-levodopa.
3. Drugs whose effect lasts much longer than the drug itself- MAO inhibitors, omeprazole.
4. Drugs with irreversible action- anticholinesterases

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Prolongation of Drug action

Advantages

- Frequency of administration is reduced more convenient.
- Improved patient compliance
- Drug effect could be maintained overnight without disturbing sleep

Method

- Prolong Drug Absorption
- Increasing plasma protein binding
- Retarding rate of metabolism
- Retarding renal excretion

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