Basic Principles of Pharmacology

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** Pharmacology

Pharmakon = Drug; Logos = Science

The study of drugs and their interactions with living systems

Wide term which includes:

- The investigation of the biochemical and physiological effects of drugs
- The study of drug absorption; distribution; metabolism and excretion
- The knowledge about the history; sources; physical and chemical properties and therapeutic uses of drugs

** Drug

- A chemical substance that is primarily used to reverse a pathophysiological defect = disease

= Virtually all chemicals may be drugs

= All drugs are toxins but not all toxins are drugs

Human
Man; Woman

Pathophysiological
Process=Disease

Management
Drugs

- **FDA approved definition of drugs**

A chemical substance that is mainly used to treat, control, prevent, or diagnose a specific disease or to prevent pregnancy!!!

- **Chemical nature of drugs**

- Acidic; Aspirin, barbiturates…etc

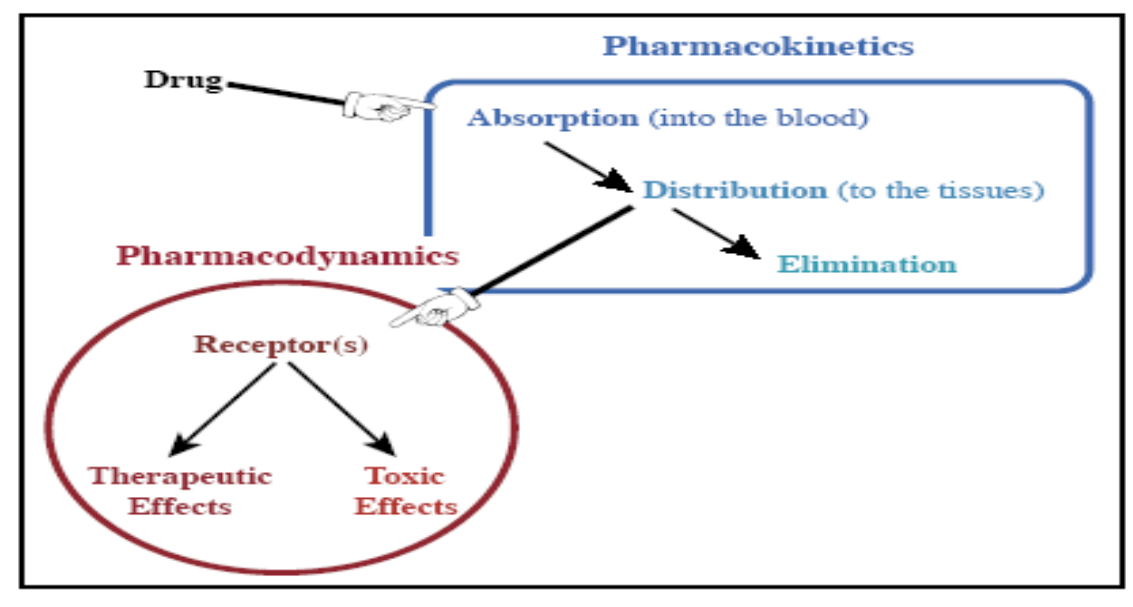
- Basic or alkaline; Morphine, Atropine, Alkaloids…etc

- Neutral; Steroids

MAJOR OBJECTIVE

TO HAVE DRUG AT SITE OF ACTION IN PROPER CONCENTRATION GOOD ENOUGH TO REVERSE DEFECT WITHOUT PRODUCING SIDE OR TOXIC EFFECTS

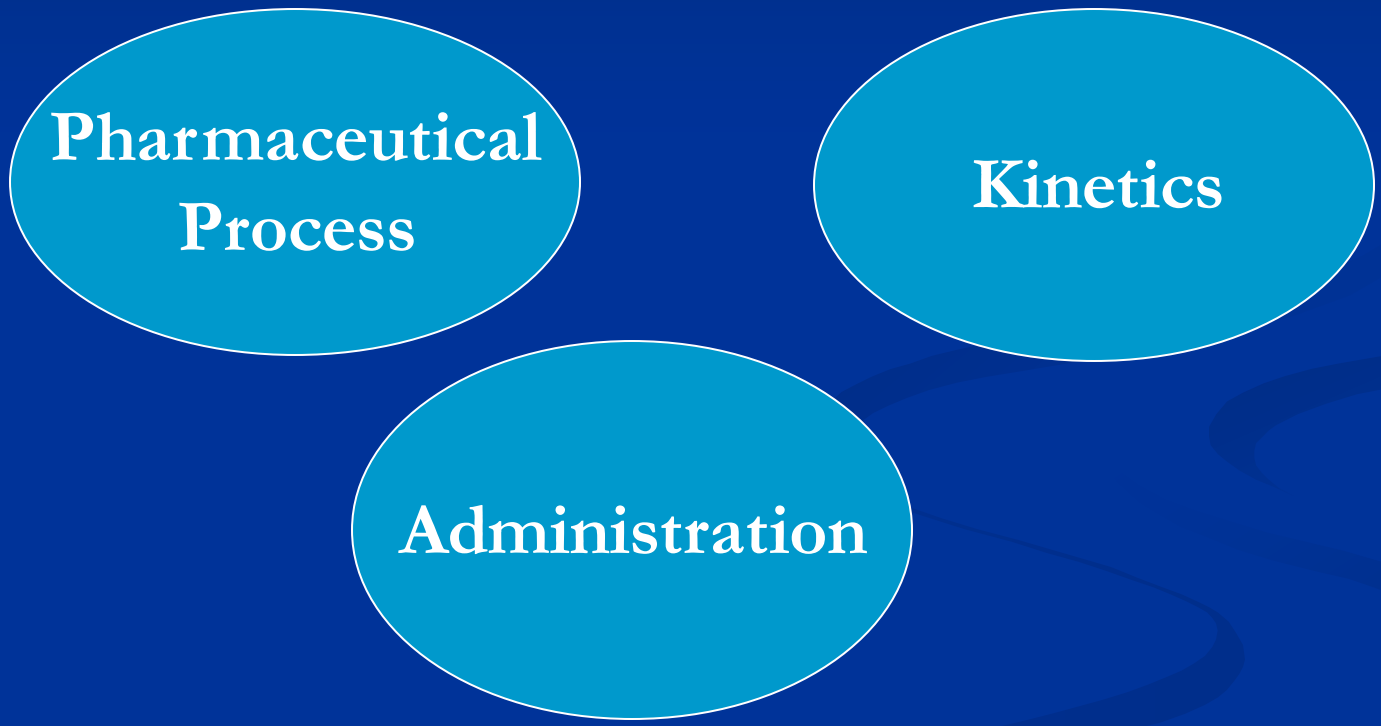
Drug discovery and pharmaceutical process



Hypothesis
=Idea

Assessment of efficacy
In vitro & in vivo studies

Assessment
of safety


Pharmaceutical Process
Kinetics
Administration

- Pharmaceutical process; drug in dosage form:

Is the drug getting into patient?

- Pharmacokinetic process:

Is the drug getting to its site of action?

- Pharmacodynamic process:

Is the drug producing the required pharmacological effect?

- Therapeutic process (clinical pharmacology):

Is the pharmacological effect being translated into therapeutic effect?

- Phrmacogenetics

Individual variations in responding to drugs + gene therapy

- **Drug discovery & development**

1. Starts with prediction=an idea & hypothesis

What helps?

- Awareness of the beneficial effects of plants and animal products (natural sources)
- Chemical identification of a wide variety of natural mediators and the possibility of modifying them chemically

e.g. epinephrine, norepinephrine
acetylcholine
histamine
prostaglandins
endogenous opioids
hormones…etc

- Avoid chemicals with highly reactive groups (toxic)

2. Design and synthesis of useful drugs or substances through simple techniques or with the help of advanced technology

e.g. a plant → fractionation, chromatographic experiments → identification of the active ingredients → isolation → purification → good drug (recently most drugs of plant source could be synthesized)

An animal → isolation of a substance (Thyroid hormones; insulin…)

Human → isolation of a substance (HMG's)

Simple peptides → a.a sequencing machine

Complex proteins → recombinant DNA technology=genetic engineering

- Receptology studies

Allowed synthesis of huge number of agonists and antagonists

3. Preclinical studies

Studies on tissues and whole animals

- Determine efficacy

Isolated tissue e.g. bronchi → organ path → testing drug…etc

Animal models

→ drug ↓ BP

→ drug ↓ blood sugar level

- Determine pharmacokinetic parameters

Absorption, distribution, metabolism…etc

- Determine pharmacodynamics (MOA)

- Assessment of drug toxicity=safety

. Acute toxicity studies

Determination of LD50; margin of safety…etc

. Subacute and chronic toxicity studies

Repeated dose studies

Daily observation of animals (wt., food and water intake ..)

Obtaining biological samples (blood; urine)

Obtaining tissues (liver; spleen; stomach …etc) for histopathological exam or studies

- Special toxicology studies

. Mutagenicity (genotoxicity) tests

Could delineate the induction of gene mutations (bacterial mutagenicity test or administration of drug to pregnant animals…etc)

Some mutations could result in the development of cancer

. Carcinogenicity studies

Not always required prior to early studies in man unless there is a high suspicion that the drug could be carcinogenic e.g. suspicion of mutagenicity; highly reactive groups on drug; histopathological abnormalities…etc

Required if the use of drug in man for more than one year or + ve mutagenic test

- **Clinical drug trials (mainly 4 phases)**

- Phase 0

Phase 0 or first-in-human trials is a recent phase approved in accordance with the United States FDA's 2006 Guidelines

Phase 0 trials are also known as human microdosing studies and are designed to speed up the development of promising drugs by establishing very early on whether the drug or agent behaves in human subjects as was expected from preclinical studies

Distinctive features of Phase 0 trials include the administration of single subtherapeutic doses of the study drug to a small number of subjects (10 to 15) to gather preliminary data on the agent's pharmacokinetics and pharmacodynamics

A Phase 0 study gives no data on safety or efficacy, being by definition a dose too low to cause any therapeutic effect. Drug development companies carry out Phase 0 studies to rank drug candidates in order to decide which has the best pharmacokinetic parameters in humans to take forward into further development

- Phase 0 studies enable go/no-go decisions to be based on relevant human models instead of relying on sometimes inconsistent animal data
- Questions have been raised by experts about whether Phase 0 trials are useful, ethically acceptable, feasible, speed up the drug development process or save money, and whether there is room for improvement

- Phase I

Involves the use of a drug in humans for the first time

It establishes dose level at which signs of toxicity first appear

Conducted on 20-80 healthy men with ages 18-45 yrs

- Usually a single dose is used initially and if no side effects exhibited, the dose is increased progressively until sufficient serum level is achieved (therapeutic level) or some toxic effects appear
- Such studies are conducted in hospital
- If no side effects result from single dose, multiple dose studies should be initiated

=bioavailability-bioequivalence studies

- Phase II

If phase I studies prove that the drug is safe to continue, the new drug is administered to patients for the first time

All patients should have only one problem (one disease)

It assesses efficacy and establishes optimal dose range in patients (dose-response studies are important)

Phase II studies are conducted on 80-100 patients (certain countries ask for 50-300 patients)

Also patients are observed for toxicity to assess safety of the drug

- Phase III

Similar to phase II but conducted on large number of patients (several hundreds to thousands; 250-1000 reasonable)

It also assesses safety and efficacy

Could detect effects/side effects not observed in phase II

- Phase IV

Post-marketing studies

Controlled and uncontrolled studies are often conducted after drug approval and marketing

It further assesses safety & efficacy of drugs

It allows for comparisons between different drugs used for the same disease

In addition, phase IV studies could provide evidence of a new use to the drug e.g.

- aspirin-antiplatelet
- sildenafil citrate-ED

Double-blind; single-blind placebo controlled studies are usually conducted

AFTER ALL THESE CLINICAL DRUG TRIALS THE DRUG IS USUALLY APPROVED BY NATIONAL OR INTERNATIONAL REGULATORY AUTHORITIES AND IS LICENSED FOR GENERAL PRESCRIBING

- **Ethics of the use of drugs in humans**
- Full detailed protocol has to be approved by the ethical committee, the institutional review board (IRB)
- All subjects should sign an informed consent form
- All subjects should be insured for life and damage

** Branches of pharmacology usually answer all of the following questions:

- How much of a drug to give? Dose
- How frequent a drug should be given? Related to the biological half-life ($t_{1/2}$)
- When to give it? Before or after meals; at bed time, PRN...
- How to give it? administration ... etc

** Administration (Routes) = Systemic or local

- Oral (tablets [IR; SR; MR)], syrups, susp...),
- Parenteral route = Subcutaneous S.C (solution), intramuscular I.M (sol.) intravenous = I.V (sol.); depo-injectable
- Buccal (tab.) sublingual (tab.) rectal (suppositories)
- Transdermal (patches); subdermal implants
- Inhalational (sprays)

** Topical = local administration

- Liquid forms (sprays, lotions, solutions = ear or ophthalmic drops, mouth washes, S.C infiltration e.g. local anesthetics...)
- Semisolid forms (creams, ointments...)
- Solid forms (suppositories, pessaries = vaginal tablet...)

ROUTES OF ADMINISTRATION OF DRUGS

ENTERAL: Via gastrointestinal tract (GIT)

Oral (Swallow)

Sublingual

Nasogastric

Rectal

PARENTERAL: Other than GIT (injection)

Intradermal

Subcutaneous

Intramuscular

Intravenous

Intraarterial

Intrathecal

Epidural

Intracardial

Intraperitoneal

Intrapleural

Intraarticular

TOPICAL / SITE SPECIFIC

Epidermal

Transdermal

Conjunctival

Inhalation

Nasal

Vaginal

Urethral

Oral route

Dosage forms:

- Tablet, Capsule, Powder, Solution, and Suspension

Advantages:

- Convenient (to most patients), self medication, cheap, relatively safe, large volume may be given, does not require maximal sterility

Disadvantages:

- Absorption is unpredictable, slow onset of action, impossible to use in unconscious or in vomiting patients, some drugs may be destroyed by gastric acidity, presence of food or other drugs may interfere with absorption. Undergoes first-pass metabolism

Rectal:

Dosage forms: Ointment, solution, suppository and Jelly

Advantages:

Avoids gastric irritation, may be used in unconscious patients or vomiting patients or who are unable to swallow. Useful in children. Avoids first-pass metabolism

Disadvantages:

Inconvenient to the patients (Discomfort), absorption is slow and incomplete, irritation and inflammation to rectal mucosa

Sublingual:

Dosage forms: Tablet, solution and aerosol

Advantages:

Rapid onset of action, not destroyed by acidity, avoids first-pass metabolism

Disadvantages:

Not suitable for large volumes, poor absorption in vomiting patients, bitter or irritant and water-soluble drugs cannot be given

Intravenous: Dosage forms: Solution

Advantages:

100% bioavailability, no absorption is required, fastest onset of action, administration of large volume of drug, avoids first-pass metabolism

Disadvantages:

Often inconvenient, require maximal sterility, self medication is not possible, difficult to reverse acute adverse effects, increased risk of infections

Transdermal:

Dosage forms: Patch

Advantages:

Used for slow continuous administration, prolonged duration of action, no first-pass effect, minimal adverse effects

Disadvantages:

Only a small number of drugs can be used by this route, slow onset of action, could lead to local reactions

Factors affecting the dose

- Age
- Weight
- Route of administration
- Sex

Factors affecting administration

- Physicochemical properties of drugs
- Site of action
- Status of patient
- Dosage interval

Drug sources:

- Natural

Plants (atropine, digoxin), animals (thyroid hormones; insulin), human (HMG's)

- Semisynthetic (many antibiotics)

- Synthetic (agonists; antagonists)

Drug nomenclature:

- Chemical name e.g. acetyl salicylic acid
- Generic name; nonproprietary; official; approved name… Aspirin

It is the name that is given to a drug according to its active ingredient that makes it work

Generic name is the most widely used in pharmacology

- Trade name; Proprietary; brand name Remine®; Bufferin®…etc

** Pharmacokinetic process

It is the study of what the body does to a drug

It includes the processes:

- Absorption
- Distribution
- Metabolism
- Excretion = elimination

Drug absorption

Passage of drug from site of administration to circulation and then distributes to reach its target organ (site of action)

Behavior of drugs in the plasma:

- **Bioavailability:**

The fraction of the given dose that gets into blood

The bioavailability of an I.V given drug is 100%

- **Protein binding:** Represents:

* A reservoir to the drug

* A mean by which drug reaches its site of action

* A major site of drug-drug interactions

Strongly bound drugs to blood proteins remain longer in blood, have longer $t_{1/2}$ & DOA

** The free form of the drug, is the form which is active and crosses membranes

(e.g. 50% of a given drug is albumin bound, means that 50% of the drug which is present in plasma is albumin bound)

Sites of drug absorption:

- Oral mucosa (buccal; sublingual tab.)
- Stomach (aspirin)
- Intestine (major site; iron; vit. B_{12})
- Lungs (general anesthetics)
- Rectum (suppositories)
- Skin (local preparations)

Factors affecting absorption:

- Drug size (Most drugs have MW's between 100 and 1,000)
- Lipid solubility (major factor)

Lipid/water partition coefficient

- Degree of ionization or environmental pH:

Henderson-Hasselbalch Equation

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

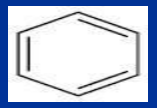
$pH = pKb + \log [BOH]/[B^+]$

Ionization of drugs is the process by which positively or negatively charged ions are formed in a solution

Most of the drugs are organic compounds (weak acids or weak bases). The organic drugs are not completely ionized in the fluid, they exist in ionized and nonionized forms

- Ionization of drugs depends on the pka of the drug and the pH of the medium
- The Ka for an acid or the Kb for a base of a molecule is a measure of its strength as an acid or base
- The pK of a drug is the pH at which the concentration of the ionized and non-ionized forms are equal (i.e. 50% ionized and 50% non-ionized)

Polar groups: O; NO_2; COOH; OH…etc

Non polar groups: - S; halogens; Ch_3; 

Non polar (unionized; lipid soluble) form crosses membranes

Polar (ionized; water soluble form is the pharmacologically active form

Example:

Sulfanilamide	Sulfathiazole	Sulfacetamide
pKa 10	pKa 7	pKa 6

At pH 7

-nilamide	0.1% I	99.9% NI
-thiazole	50% I	50% NI
-cetamide	99% I	1% NI

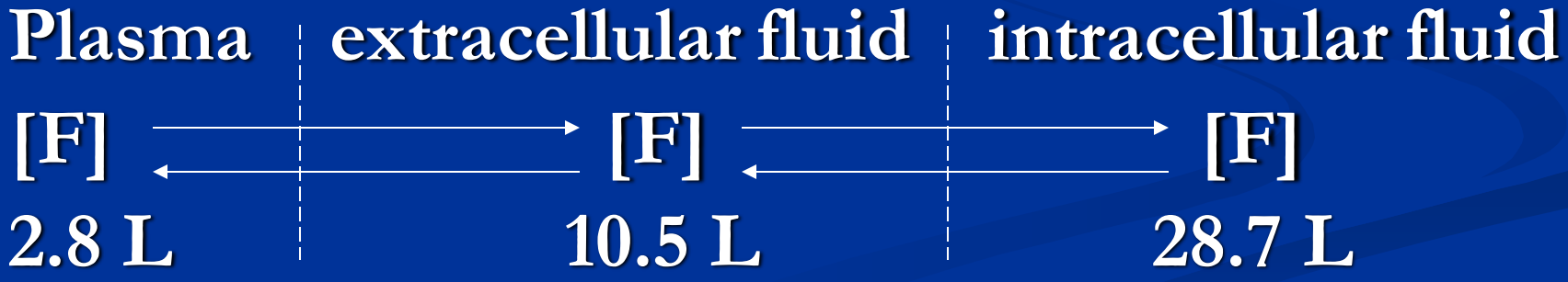
Cont. factors affecting absorption:

- Concentration of drug = dose
- Surface area of absorption
- Blood circulation to absorbing area
- Route of administration (I.V the fastest)
- Dosage forms
- Food

Drug distribution

Passage of drugs from blood to different tissues (site of action) Extent of distribution could be measured by a constant known as AVD

70 Kg man 60% H_2O ≈ 42 liters



Apparent volume of distribution **(AVD)**:

The total volume in which the free form of a given drug distributes in different body compartments at equilibrium

$$AVD = \text{Dose (mg)} / C_0 \text{ (mg/L)}$$

C_0 = Concentration of drug in blood at time zero

- Highly lipid soluble drugs e.g. digoxin, have a very high Vd (500 liters)
- Drugs which are lipid insoluble e.g. neuromuscular blockers, remain in the blood, and have a low Vd
- Very very high Vd indicates extensive tissue binding

Factors affecting drug distribution:

- Compartmental selectivity
- Organ selectivity
- Protein binding (Major factor)
- Natural barriers
    - BBB
    - Placenta
    - Mammary glands

A low Vd

Usually denotes that the drug is mainly in the plasma i.e. high plasma concentration and low tissue distribution and binding

A High Vd

Indicates significant distribution or uptake by many tissues

A high Vd is commonly associated with very long half-life to a given drug

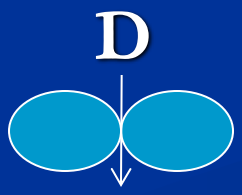
High or extensive plasma protein binding may result in:

- Restricted drug distribution
- Reduced intensity of pharmacological effects
- Predisposes the drug to many interactions
- Increases drug's duration of action (half-life)
- Decreases drug's AVD

Mechanisms of drug transfer across membranes:

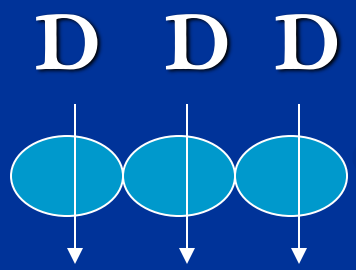
- Simple diffusion

Crossing through water pores of membranes, no energy or carrier required, from high to low concentration, drugs with low M.W (must be lipid soluble and concentration gradient is the driving force)



- **Passive diffusion (major mechanism)**

Crossing through cells or the lipid bilayer, no energy or carrier required, from high to low concentration



The only requirement for passive diffusion is that the drug should be lipid soluble

- Facilitated diffusion

Requires a carrier, no energy required, from high to low concentration

- Active transport

Requires energy ± carrier, could be from low to high concentration

(Facilitated diffusion and active transport follow saturation kinetics because No. of carriers is limited)

- Endocytosis

Phagocytosis (solid particles)

Pinocytosis (fluid particles)

Drug metabolism

A change in the chemical structure of the drug, or addition of a hydrophilic groups to an initially lipophilic drug until it becomes sufficiently ionic so as to be easily filtered and excreted by the kidneys

The rate of metabolism (K_m) of a given drug depends upon the chemical characteristics of the drug and has nothing to do with the benefit or harm of the drug

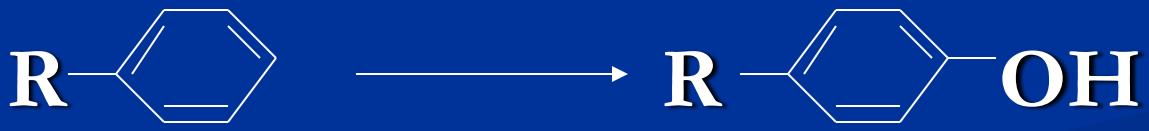
Drug metabolism involves 2 major pathways:

1. Pathway I = Oxidation reduction reactions

Also known as mixed function oxidase system and cytochrome P_{450} system (CYPs=A;B...)

Examples:

. Aromatic hydroxylation

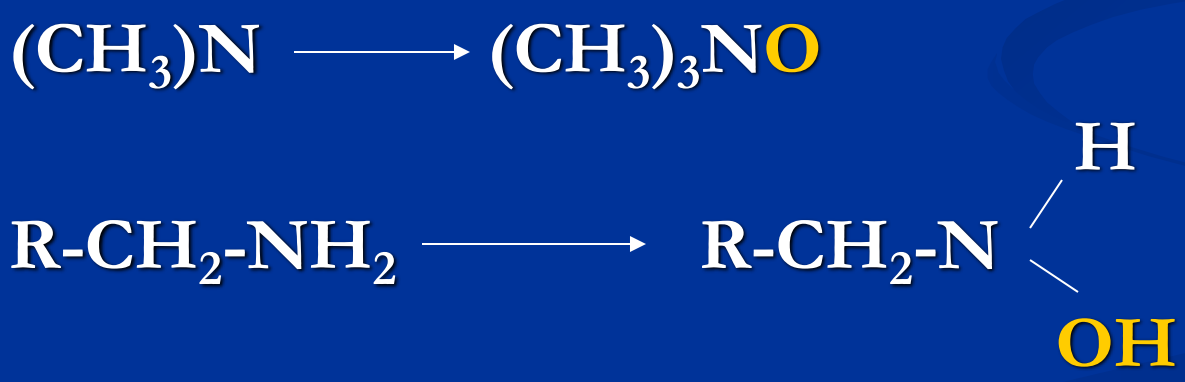


. Aliphatic hydroxylation

. O-dealkylation

. N-dealkylation

. N-oxidation; N-hydroxylation



. Sulfoxidation

. Hepatic reduction

Azo reduction

$R_1\text{-}N{=}N\text{-}R_2 \longrightarrow R_1\text{-}NH_2 + H_2N\text{-}R_2$

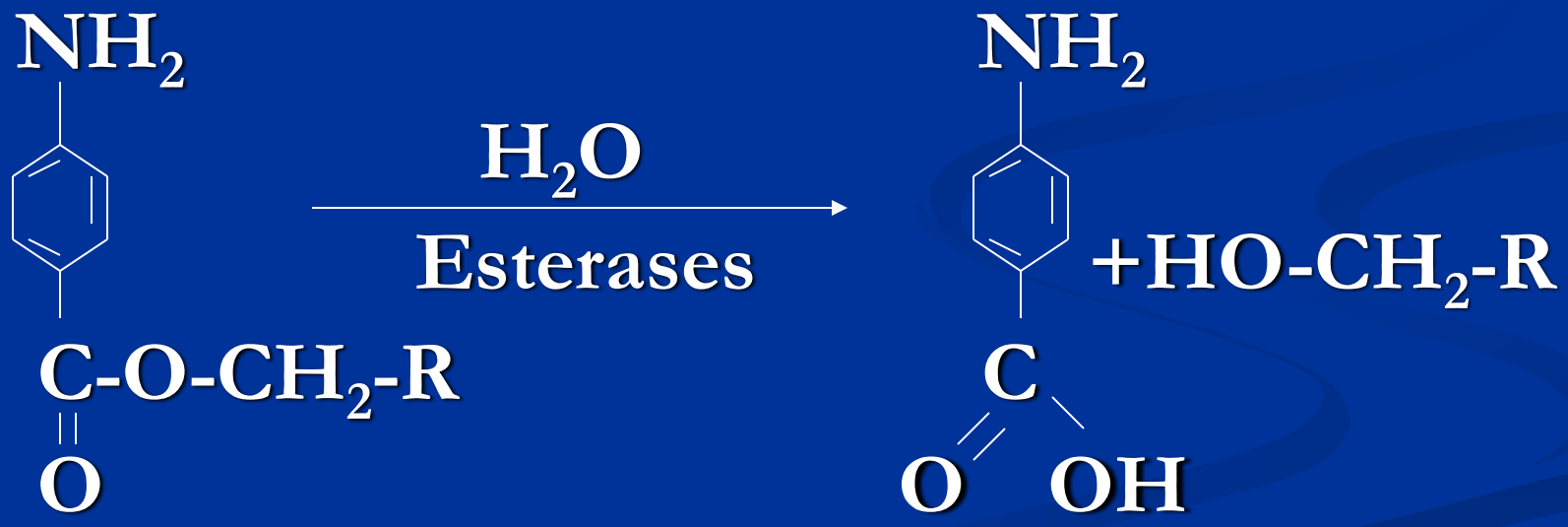
Nitroreduction

$R\text{-}NO_2 \longrightarrow R\text{-}NH_2$

- Nonmicrosomal oxidation and reduction

Alcohol oxidation; chloral hydrate reduction

- Hydrolysis reactions



2. Pathway II = Conjugation reactions

Addition of certain groups to a drug to become more polar and readily excreted

soluble enzymes in cytosol

Acceptor + Donor ⟶ conjugate

(Drug) (activated) of liver (transferases)

- Metylation
- Acetylation
- Glucuronic acid conjugate
- Etheneal sulfates
- Glycine conjugate (mercaptopuric acid formation)


Inactive D
*Active D
kidney
I
II
I
II
II
I

Characteristics of an ideal metabolite:

- Water soluble
- Pharmacologically inactive
- Not to be toxic

Sites of drug metabolism:

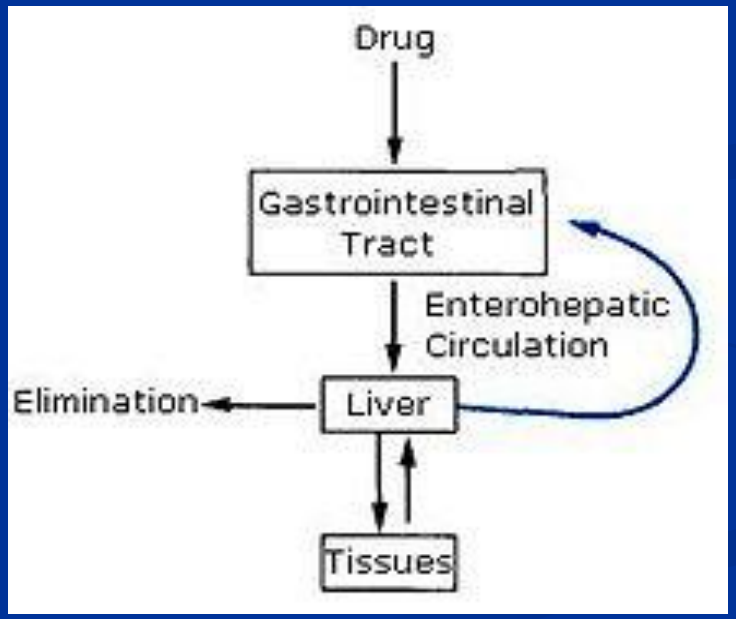
- Liver (major site)
- Intestine
- Lungs; brain; kidney; plasma, adrenals…etc

Factors affecting drug metabolism:

- Genetic factors and species differences (major factor) (slow and rapid metabolizers)
- Sex
- Drug-drug interactions
- Age (paracetamol vs chloramphenicol)
- General health of patients and nutritional status
- Dose and frequency of administration

First-pass effect = rapid metabolism

Enterohepatic circulation



Inducers

Barbiturates

Theophylline

Phenytoin

Rifampicin

Allopurinol

Smoking

Inhibitors

Ketoconazole

Fluconazole

Cimetidine

Erythromycin

Contraceptives

Diltiazem

Grape fruit juice

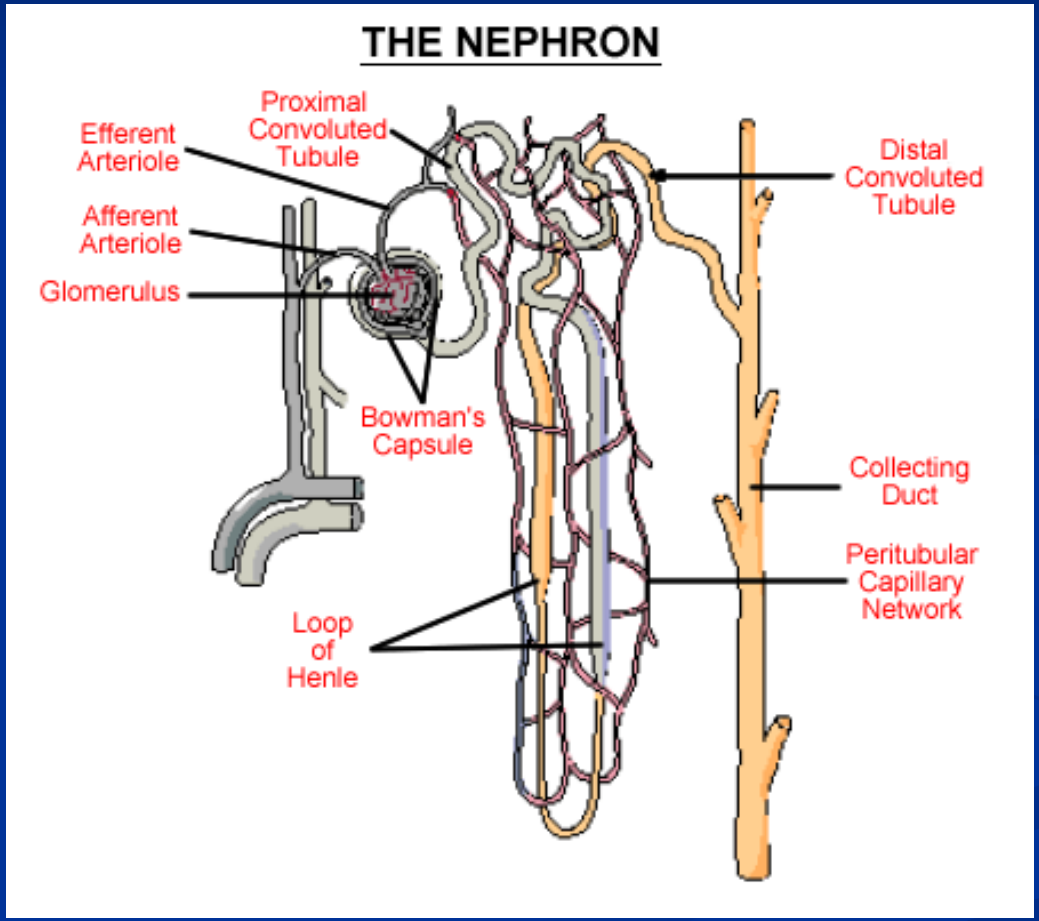
Drug excretion = elimination

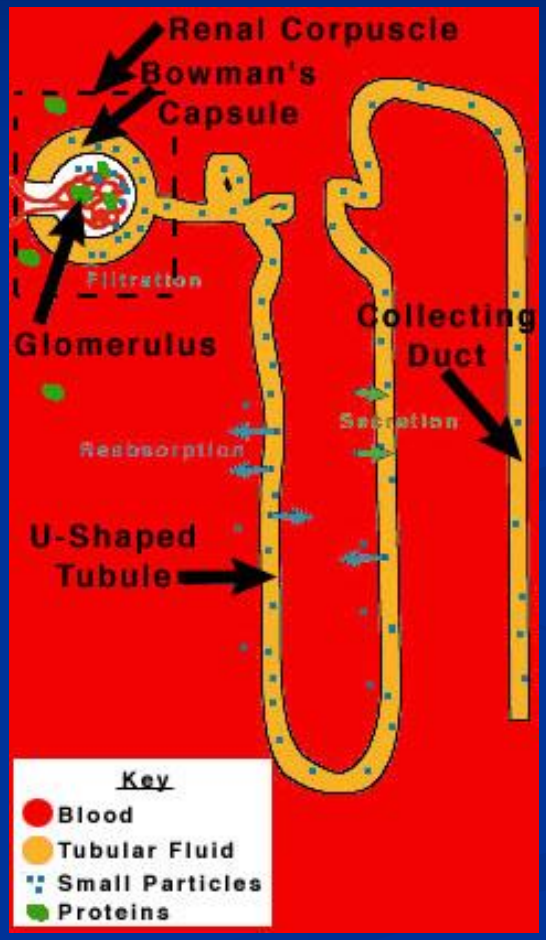
A process by which a drug or it's metabolites are eliminated from the body

Major sites:

- Kidney (most drugs)
- Liver

Kidney function (old people)!!!!!


THE NEPHRON
Proximal Convoluted Tubule
Efferent Arteriole
Afferent Arteriole
Glomerulus
Bowman's Capsule
Distal Convoluted Tubule
Collecting Duct
Peritubular Capillary Network
Loop of Henle


Renal Corpuscle
Bowman's Capsule
Filtration
Glomerulus
Collecting Duct
Secretion
Reabsorption
U-Shaped Tubule
Key
Blood
Tubular Fluid
Small Particles
Proteins

Methods of excretion:

- Filtration
- Tubular secretion

- Specific secretory mechanism for weak acids and another one for weak bases (80% of drugs are excreted by this mechanism)
- Still some drugs remain lipophylic so could be reabsorbed (this could be inhibited by changing pH and provides the use of alkali in enhancing excretion of acidic drugs)

Probenecid

Penicillin

The rate of excretion of a given drug is determined by a specific constant known as K_e which depends on AVD and clearance

$$\text{Clearance} = \frac{U_x \text{ (mg/ml)} \times V}{P_x \text{ (mg/ml)}}$$

Renal clearance is the volume of plasma cleared of drugs per unit time

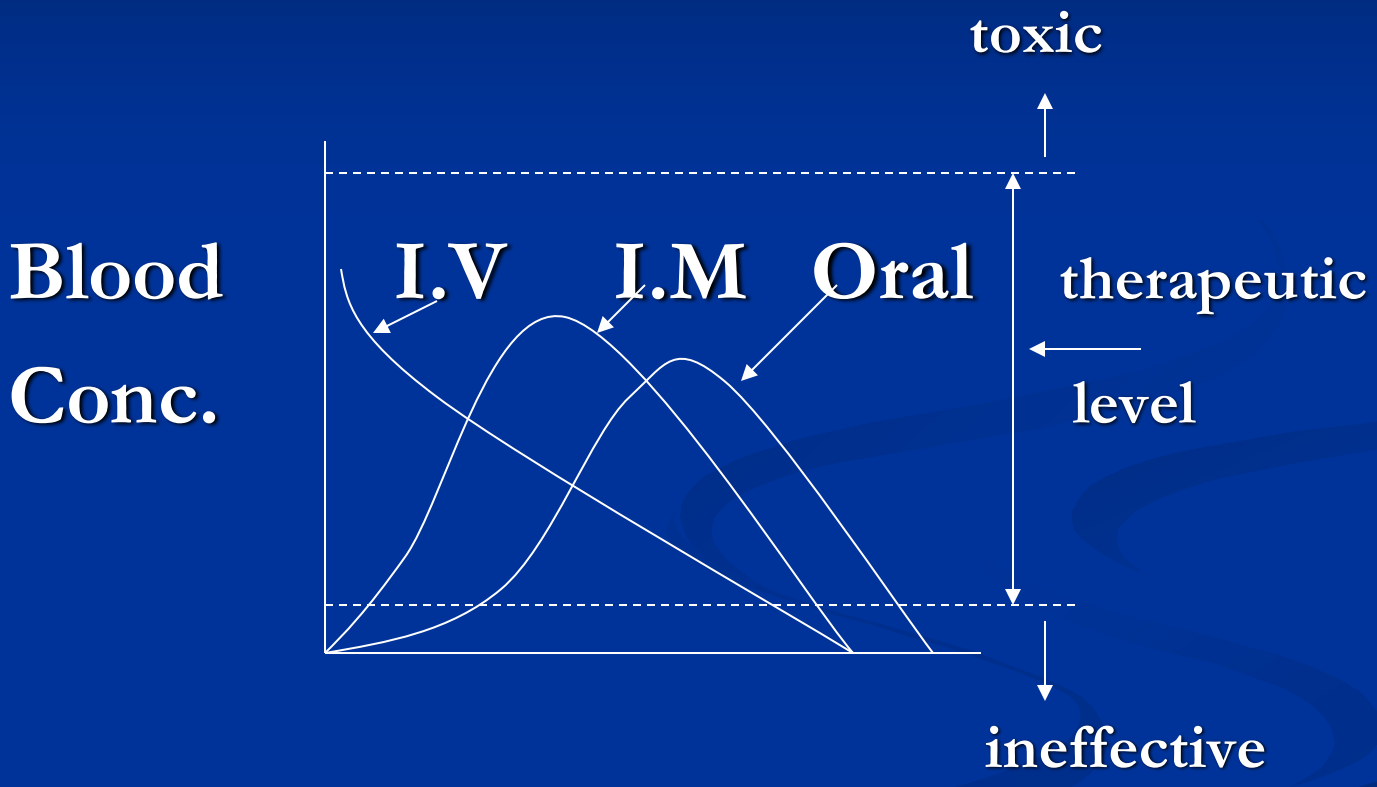
K_e = Clearance (ml/min)/AVD (ml)

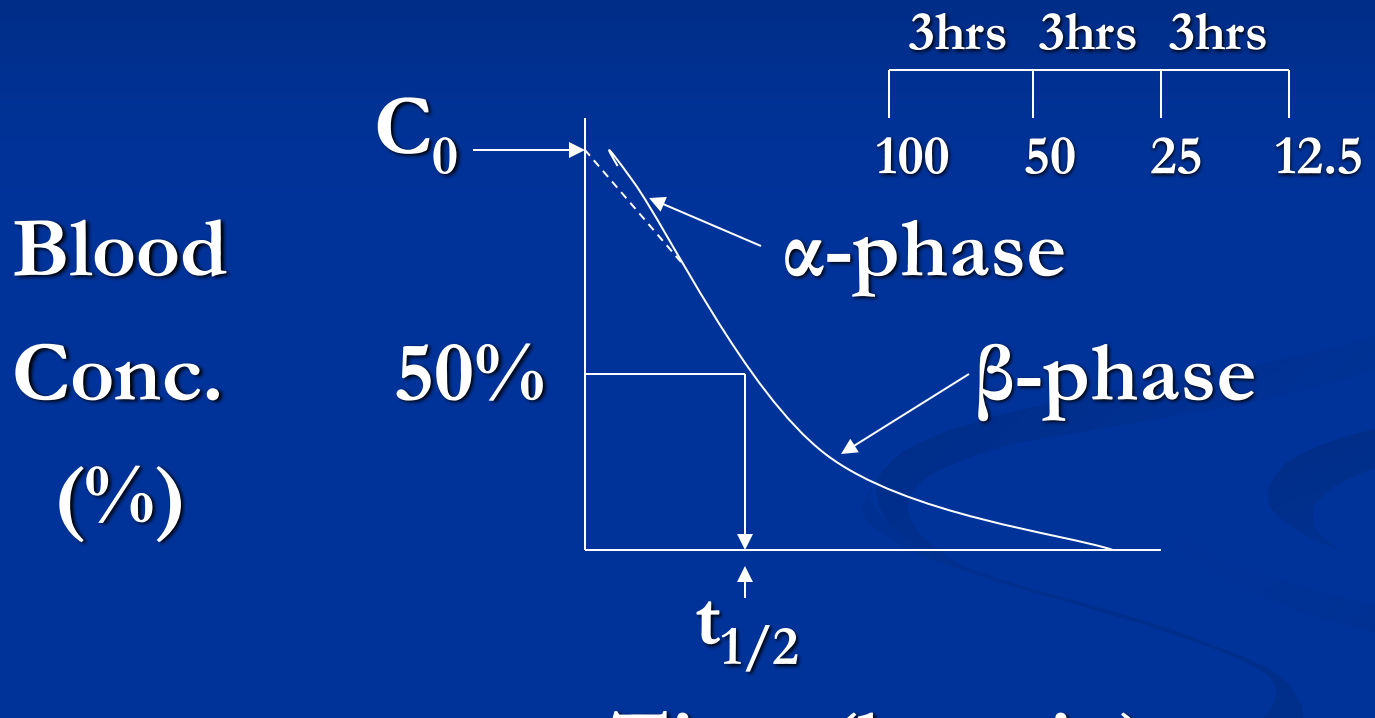
Ke unit: min^{-1} = 1/min

$K_e = 0.693/t_{1/2}$ (min)

$t_{1/2}$ = o.693 × AVD/clearance

$K_T = K_m + K_e$


toxic
Blood
Conc.
I.V
I.M
Oral
therapeutic
level
ineffective
Time (hr; min)


3hrs 3hrs 3hrs
100 50 25 12.5
C_0
α-phase
β-phase
Blood Conc. (%)
50%
$t_{1/2}$
Time (hr; min)

Steady state level (chronic administration)

Plateau

Blood Conc.

input=output

Time

Reached after 5 $t_{1/2}$ lives

Loading dose (initial large dose) followed by maintenance dose e.g. digitalization...etc

Steady state level could be calculated from this equation:

$$\bar{C}p = \frac{f \cdot D}{AVD \cdot K_e \cdot T} = 1.44 \times \frac{f \cdot D}{AVD} \times \frac{T_{1/2}}{T}$$

$\bar{C}p$ = Average steady state plasma conc. of drug

f = fraction of dose absorbed; bioavailable fraction

D = dose of given drug

K_e = first order reaction rate constant

AVD = apparent volume of distribution

T = time interval between doses

$T_{1/2}$ = biological half-life

1.44 = 1/0.693

Trough and peak drug levels:

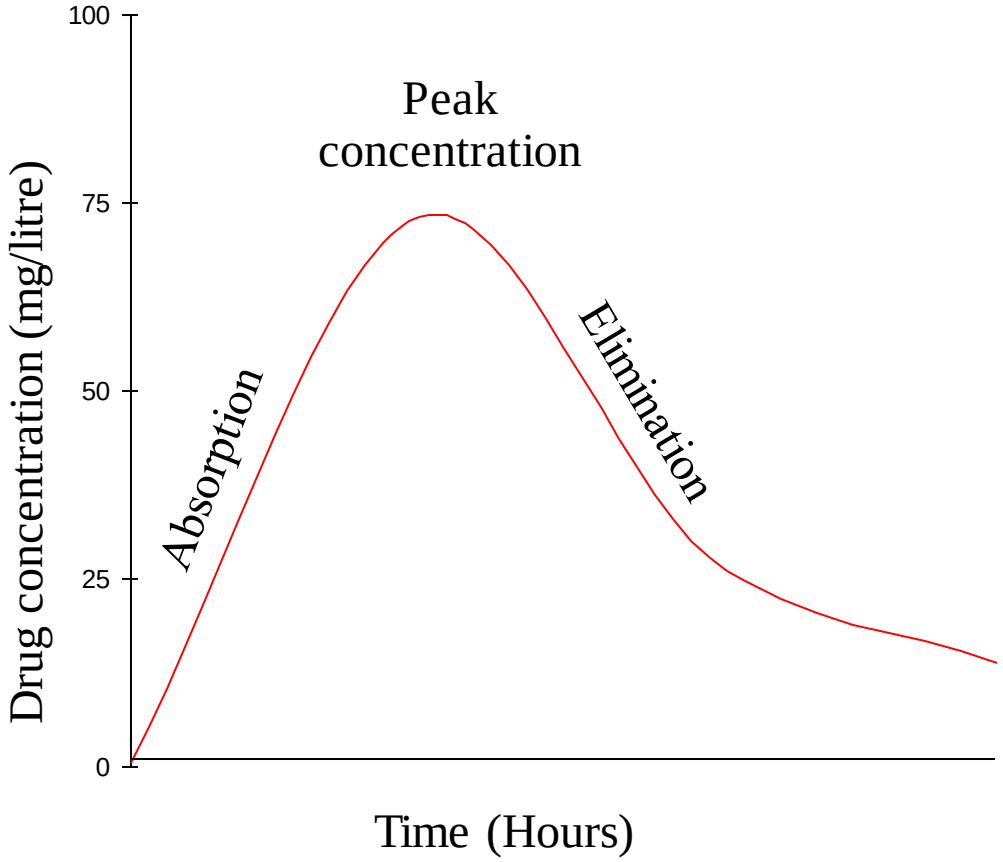
Used to establish the effectiveness of a drug

Trough is the lowest drug level that is needed to reach therapeutic range

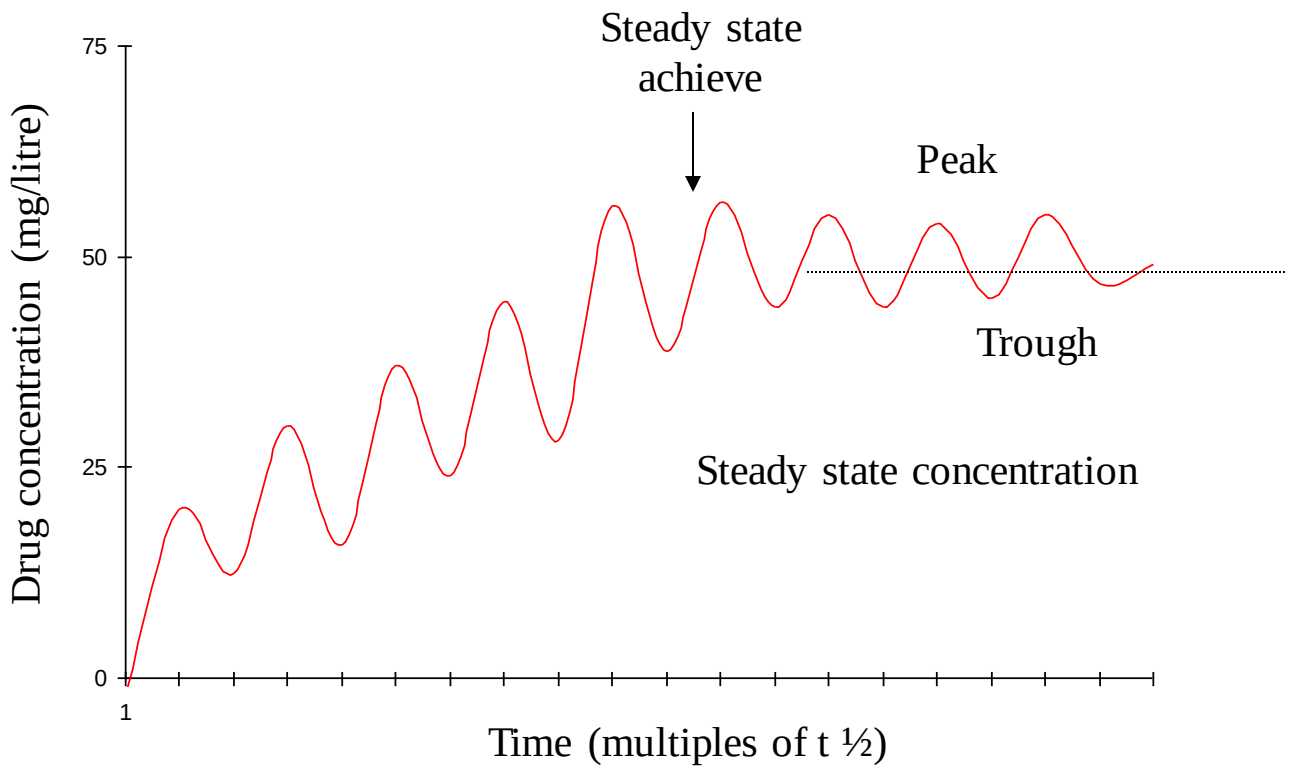
Peak is drawing the serum blood levels (30 min parenteral; 1-2 hr oral) after the drug is administered

Trough is drawing the serum blood levels right (30 min-1 hr) before the next dose

(If trough or peak levels are > than normal, the patient is at risk for adverse effects)



Plasma concentration-time curve following a single oral dose



Plasma concentration of a drug given at half-time intervals steady state is achieved after five doses

Bioavailability-bioequivalence studies:

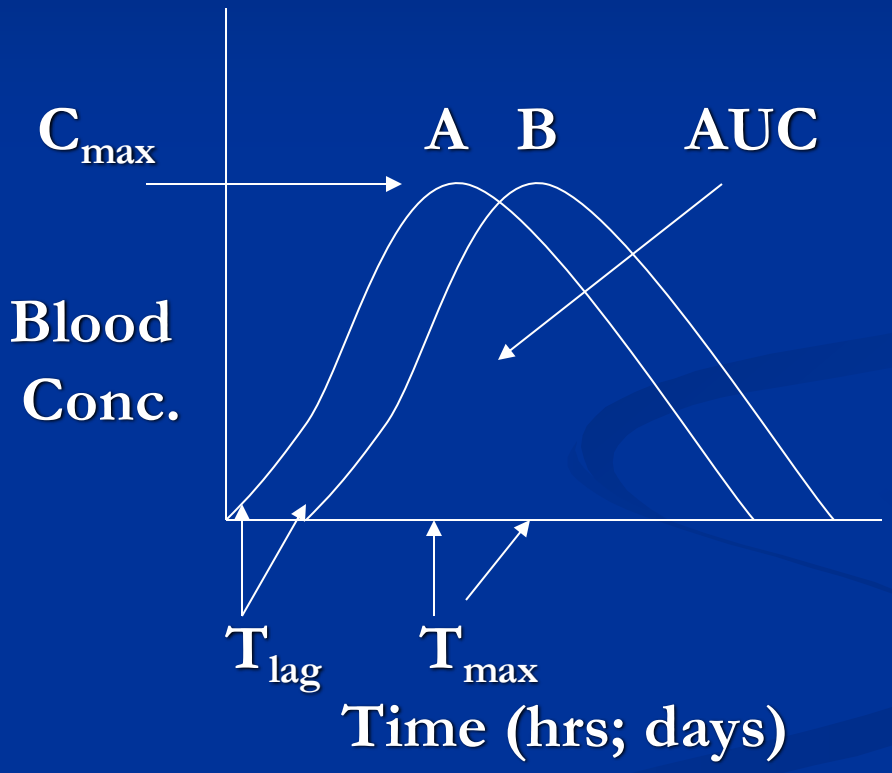
To prove that 2 drugs have the same

- Chemical structure

- Bioavailability

- Biochemical activity

- Therapeutic effects



K_T; K_m; K_e; $T_{1/2;}$ clearance...etc

Terms and definitions

- Dose

It represents the amount of a drug to produce an effect

- Therapeutic dose

A dose which is required to produce a therapeutic effect

- Toxic dose

The dose which produces a toxic effect

- Half-life ($t_{1/2}$)

It is the time by which plasma concentration of a drug falls or declines by 50% of its maximum concentration

- Steady state concentration

It is the concentration of a drug at which the rate of administration is equal to that of elimination of that drug. It usually takes 5 to 6 half-lives of a drug

- Loading dose

A large initial single or multiple doses are given for some drugs to achieve a rapid steady state concentration

- Maintenance dose

The dose which is used to maintain the steady state concentration or to maintain the therapeutic effect of a drug. It is given at a fixed interval time

- Tolerance

When repeated administration of an equal doses of a drug for a prolonged period of time (chronic administration) results in decreased responses. Original responses can be obtained by increasing the dose (e.g. drugs of addiction)

- Tachyphylaxis

Rapidly developing tolerance. When repeated administration of a drug produces decreased responses within a short period of time (even with 2 or 3 doses). This phenomenon is usually observed in the laboratory

- Capacity limited processes

1. First-order (exponential) kinetics

All pharmacokinetic processes (abs., distr., met. excr.) occur at a rate directly proportional to conc. of drug e.g. increasing dose increases these processes

2. Zero-order (saturation) kinetics

Apply mainly to met. and elimination where their rates reach saturation (maximum) and a further increase in rates is impossible despite an increase in dose (these processes are independent of the conc. (absorption from SR tab. or continuous infusion are good examples)

First order kinetics may become zero order when high conc.'s of drug are present

First-order kinetics:

It represents that the rate of elimination of the drug from the body is proportional to the concentration of the drug in the plasma or blood

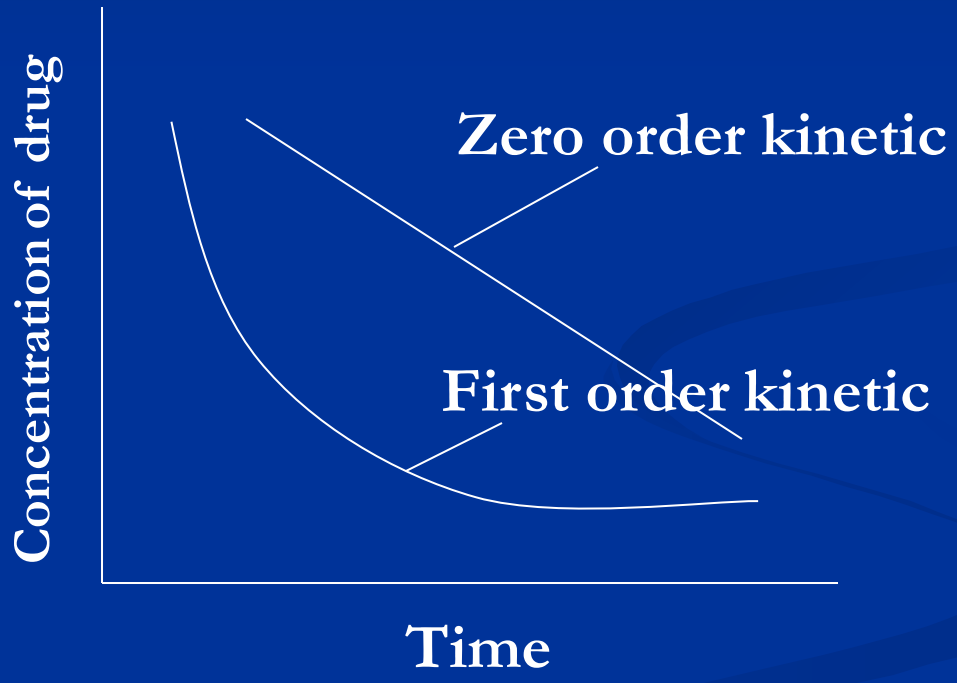
A percentage of the drug is eliminated per unit time. Half-life of the drug is constant irrespective of the doses used. Most of the drugs are eliminated by this process. The curve is exponential

Zero-order kinetics:

The rate of elimination is not proportional to the concentration in the blood or plasma. A certain fixed amount of the drug is eliminated per unit time

This process is saturable and half-life may be increased if the dose of the drug is increased. A few drugs follow this process. The curve is a straight line i.e. not exponential

ORDER OF KINETICS



- Indications

Clinical uses of drugs

- Contraindications

Situations when not to use drugs

- Idiosyncrasy

Abnormal responses to a drug due to genetic (heriditory) abnormality. Rapid acetylators show therapeutic failure while slow acetylators show toxicity to a drug

- Drug interactions:

The effect of one drug on another. Takes many forms:

↑ or ↓ absorption; ↑ or ↓ protein binding; ↑ or ↓ metabolism; ↑ or ↓ excretion; ↑ or ↓ toxicity; ↑ or ↓ binding to receptors… etc

** Rule: one drug is better than two; two drugs are better than three…etc

- Side effects and drug toxicity

Unwanted, untoward, undesirable, adverse reactions to a given drug

Drugs are intended to produce a specific effect. But no drug is specific in its action. Thus, the additional, unwanted effects that are observed in addition to the desired effect of a drug, is called adverse drug effects

- Types of side effects

Type A: It is the extension of known pharmacological effect of a drug e.g. dry mouth after atropine administration

Type B: It is unrelated to the known pharmacological actions of a drug e.g. hypersensitivity reactions to penicillins (hypersensitivity reactions or drug allergy are abnormal responses to a drug due to immunological mechanism. Previous exposure to the offending drug is required)