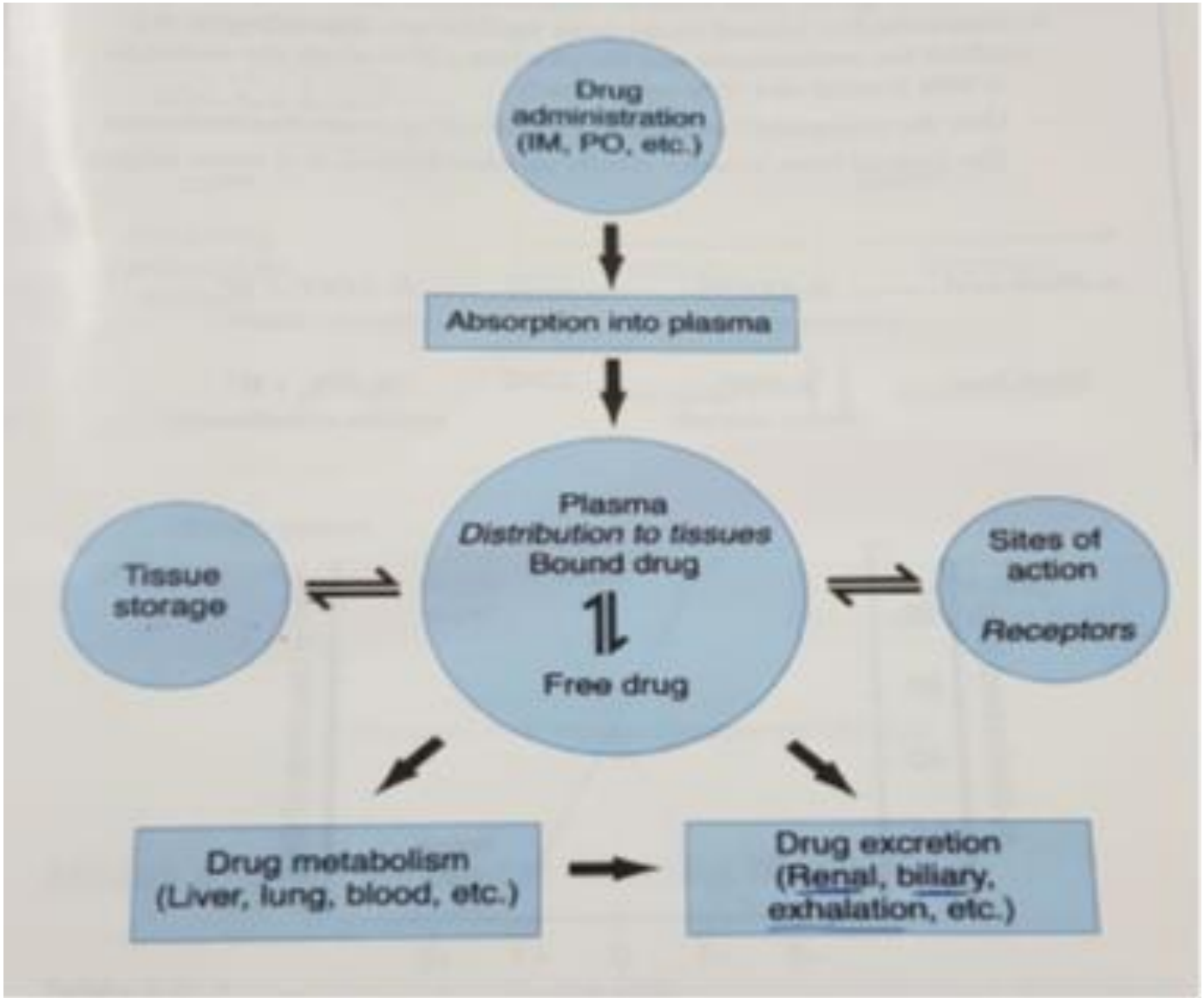
Lab2
Clinical Parameters in Drug Pharmacokinetics

Pharmacokinetics: Represents the effects of the body on drugs.
That means how the body will absorb, distribute, metabolise and eliminate the drug.



Absorption: Is the transfer of a drug from the site of administration to the blood stream.

The rate and extent of absorption depend on:

1.the environment where the drug absorbed (e g PH of GIT weak acid drug in stomach absorbed in highly acidic stomach, weak base drug absorbed in intestine with alkaline PH 7. 5

2.Nature formulation of drug (particle size, enteric coating)

3.Drugs dosage form (syrup absorbed faster than tablet)

4. ↑ Blood flow at site of absorption. ↑absorption

5.Total surface area available for absorption**:** the intestine has a surface area about 1000- fold that of the stomach, making absorption of the drug across the intestine more efficient.

6-Contact time at the absorption surface**:** If a drug moves through the GI tract very quickly, as can happen with severe diarrhea, it is not well absorbed

7.Route of administration (which influences bioavailability) Route of administration other than intravenous may result in partial absorption and lower bioavailability

Distribution: the process of distribution of drug from systemic circulation to organs and tissue . The blood, body water, extracellular, lymphatic cerebrospinal fluids are involved in movement of drug through the body.

Depending upon its(drug) chemical and physical properties, drug bounding to plasma protein or dissolved in body tissue fat, delaying its progress to its site of action, metabolism or excretion.

Protein binding:

• A drug's efficiency may be affected by the degree to which it binds to the proteins within blood plasma. The less bound a drug is, the more efficiently it can traverse cell membranes or diffuse. Common blood proteins that drugs bind to are: Albumin, lipoprotein, glycoprotein, and α, β, and γ globulins.

• A drug in blood exists in two forms: bound and unbound:

Protein + drug ⇄ protein-drug complex.

• Unbound fraction which exhibit pharmacologic effects and may be metabolized and or excreted.

Bound drug is have no action

Factor affecting on the plasma protein binding :-

1-displacement of one drug by another drug ex.: aspirin and warfarin →aspirin displace the warfarin due to high affinity to plasma protein→ high free active warfarin →↑ the toxicity of warfarin.

2.↓in the albumin plasma protein due to liver disease lead to ↑the free active drugs→ ↑ toxicity

Metabolism:

Is a biochemical modification of one chemical form to another, occurring usually through specialized enzymatic systems.

All organisms are exposed to foreign chemical compounds (Xenobiotics) in air, water and food. To ensure elimination of pharmacologically active xenobiotics as well as to terminate the action of many endogenous substances, evolution has resulted in metabolic pathways that alter their activity and their susceptibility to excretion.

* The most important organ for drug metabolism is the liver. The kidneys play an important role in the metabolism of some drugs, a few drugs (e.g. esters) are metabolized in many tissues (liver, blood, intestinal wall) because of the broad distribution of their enzymes.

Kidney cannot efficiently excrete lipophilic drugs that readily cross cell membranes and are reabsorbed in distal convoluted tubules.

Therefore lipid-soluble agents are first metabolized into more polar (hydrophilic) substances in the liver via two general phase I and phase II reactions

Phase I involve reduction, oxidation, hydrolysis

Phase II : consist of conjugation reactions.

If the metabolite from phase I is sufficiently polar it can be excreted by kidney.

many phase I metabolites are still too lipophilic to be excreted as subsequent conjugation reaction with an endogenous substrate as

glucuronic acid,

sulfuric acid,

acetic acid or

amino acid

result in polar, more water soluble

CYP 450 :

cytochrome P 450 system is important for drug metabolism and endogenous compounds (lipids) Located in most cells but primarily in the liver and GI tract. Phase I reactions most frequently involved in drug metabolism are catalyzed by CYP 450

1)Enzyme induction:

increase synthesis of cytochrome P450 enzymes in the liver that cause increase metabolism of drugs(↓ therapeutic effect of drugs). Many drugs cause this induction of enzyme: phenobarbital, phenytoin, and rifampicin , carbamazepine.

2) Enzyme inhibition:

The most likely inhibitors of drug metabolism are amiodarone, cimetidine, furanocoumarin present in grapefruit juice, erythromycin, ketoconazole, chloramphenicol , ciprofloxacin.

Inhibition of drug metabolism can lead to significant increase plasma drug concentration and adverse effects or toxicity.

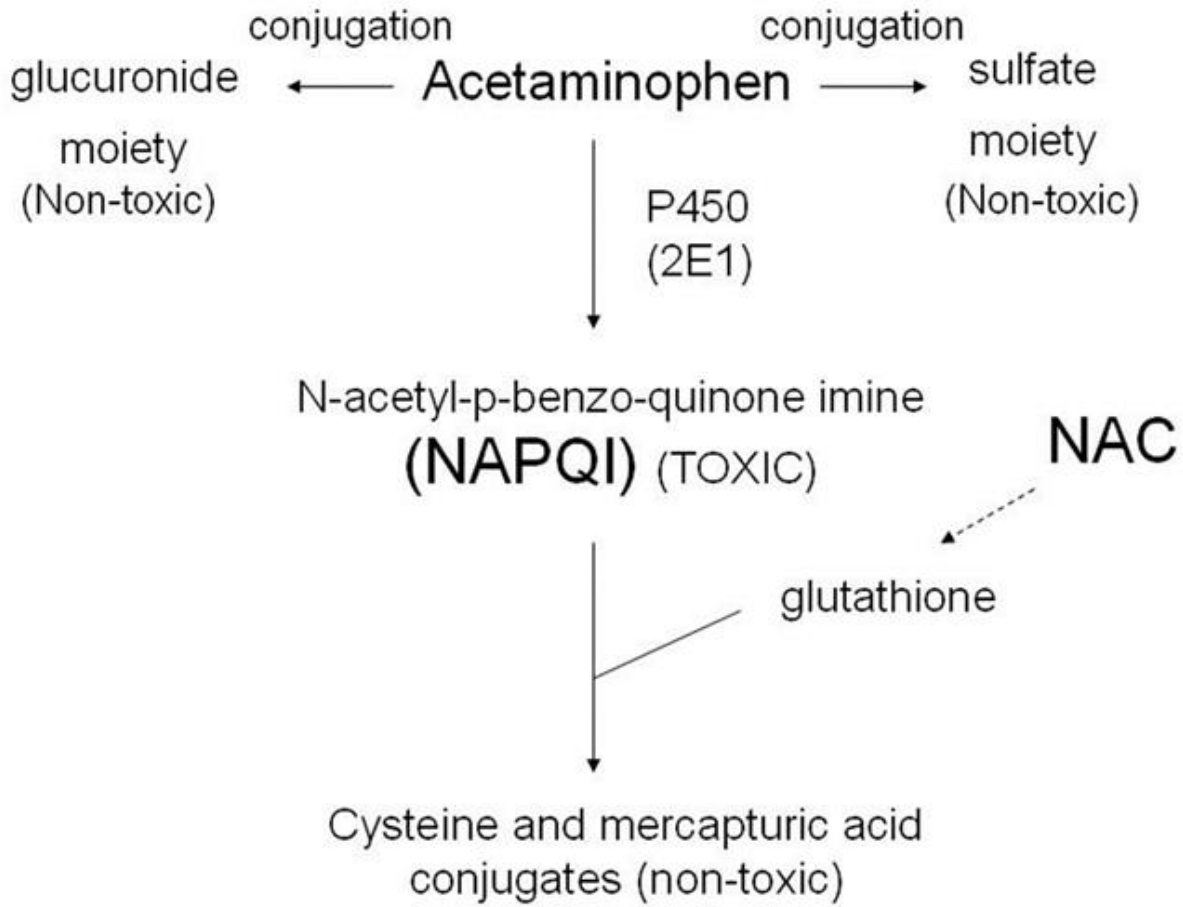
Toxic metabolism: some drugs are converted to active product by metabolism , **acetaminophen** when taken in large overdose.

- Acetaminophen is conjugated to harmless glucuronide and sulfate metabolites in case of taken in recommended dose.

-If large overdose is taken however a P450 dependent system converts some of the drug to reactive intermediate (N-acetyl-p-benzoquinone imine) this intermediate is conjugated with glutathione to a third harmless product. If glutathione stores are adequate.

-If glutathione stores are exhausted, however, the reactive intermediate combines with sulfhydryl groups on essential hepatic cell proteins, resulting in cell death.

- Prompt administration of other sulfhydryl donors (e.g. acetylcysteine) may be lifesaving after overdose.



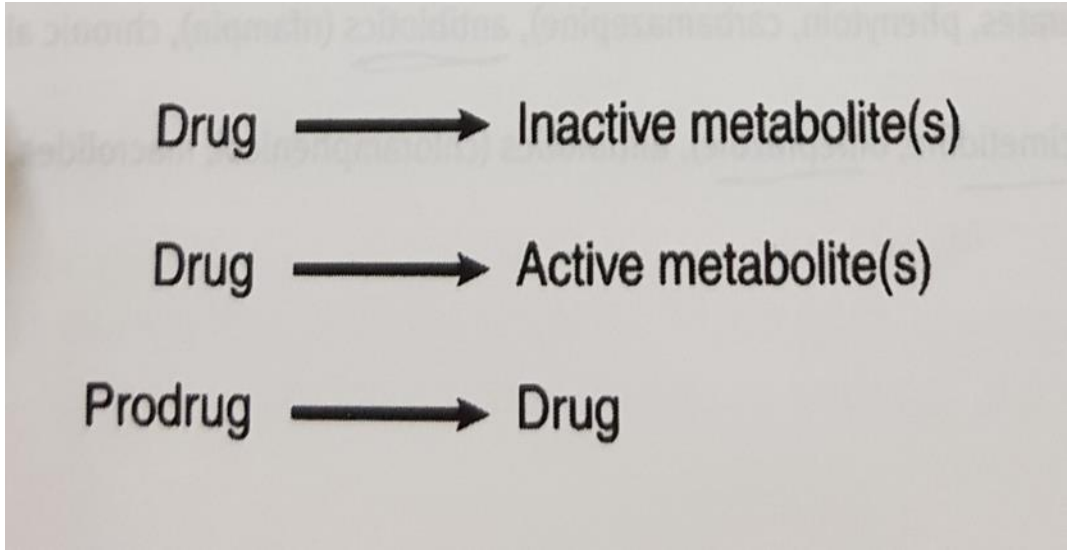
Acetaminophen metabolism

Drug metabolism as mechanism of drug activation:

Prodrug: are inactive as administered and must be metabolized in the body to become active as (levodopa).

- Many drugs active as administered and have active metabolites as well (some benzodiazepines).

- Some drugs (lithium) are not modified by the body they continue to act until they are excreted.



First pass metabolism:

Following absorption across the gut wall, the portal blood delivers the drug to the liver prior to entry into the systemic circulation a drug can be metabolized in the gut wall (CYP3A4) enzyme system, but most commonly in liver. Any of these sites can contribute to this reduction in bioavailability.

First-pass metabolism by the intestine or liver limits the efficacy of many oral medications. For example, more than 90% of nitroglycerin is cleared during first-pass metabolism. Therefore, it is primarily administered via the sublingual or transdermal route. So, drugs that extensively metabolise by liver or intestine should be given in doses sufficient to ensure that enough active drug reaches the desired site of action

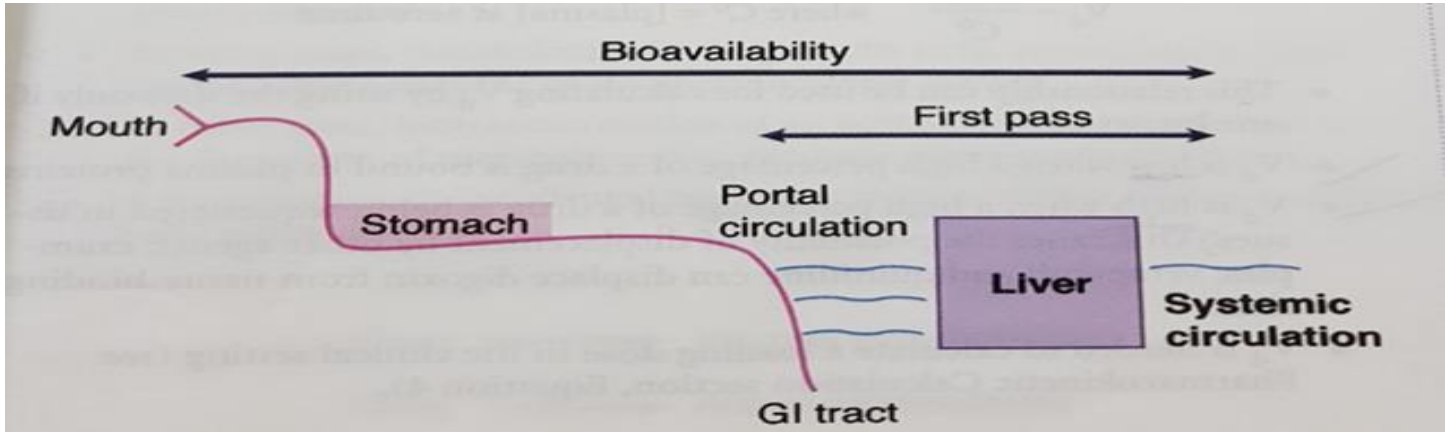


Figure I-1-6. Bioavailability and First-Pass Metabolism

Elimination :Removal of drugs and their metabolites from the body using either the primary elimination route or secondary.

The kidney is the most important organ for excretion of drugs.

-many other routes of excretion bile ,lung, sweat, saliva, breast milk ,faeces play a minor role.

-exhalation of volatile anesthetics

Important of studying pharmacokinetics parameters

Pharmacokinetic parameters can help clinicians in designing the optimal drug regimens by selecting the suitable:

Route of administration, dose, frequency and duration of treatment.

Dose-response curve: Is a simple relationship between the X-axis, which represented by the dose of the drug, and the y-axis that reflect the receptors' response or the drug effect (figure 1).

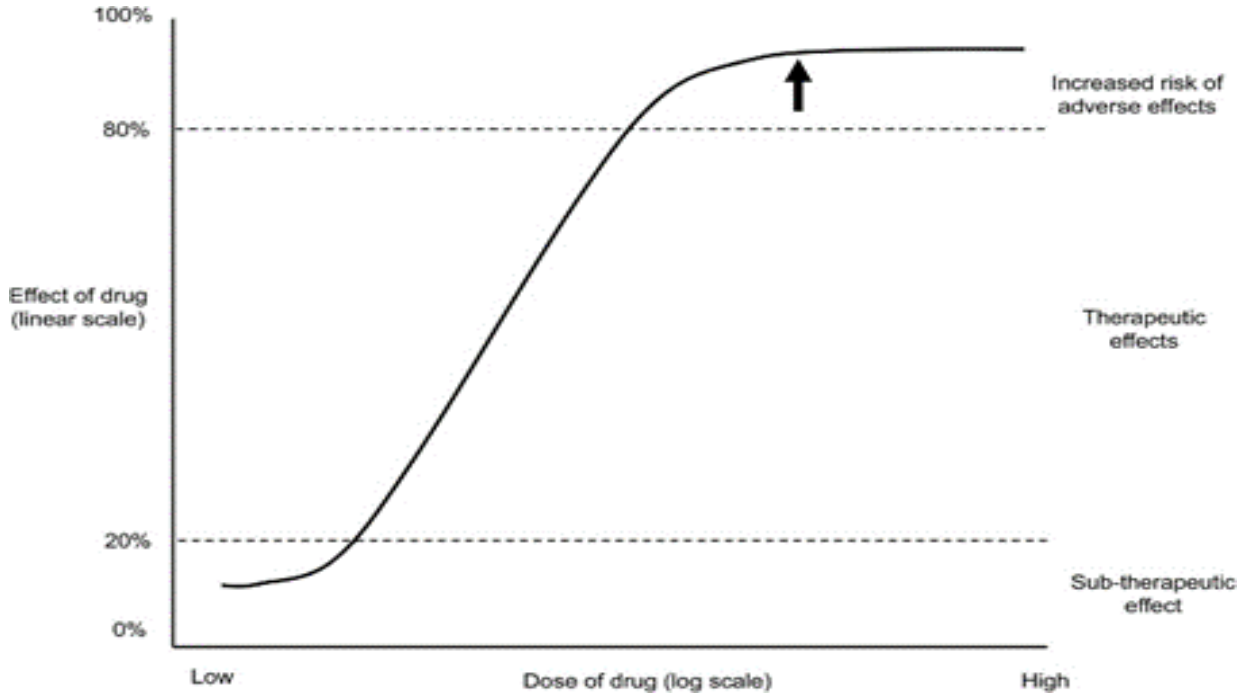


Figure 1: Drug-response curve

Pharmacokinetic parameters:

I-Area under the Drug Concentration Curve (AUC):

Is the area under the plot of plasma concentration of a drug versus time after dosage (Figure 2). Its importance is embodied in providing an insight into the extent of exposure to a drug and its clearance rate from the body. It is required by the FDA in the drug approval process. The usual unit is amount. time/ volume (mg.hr/L).

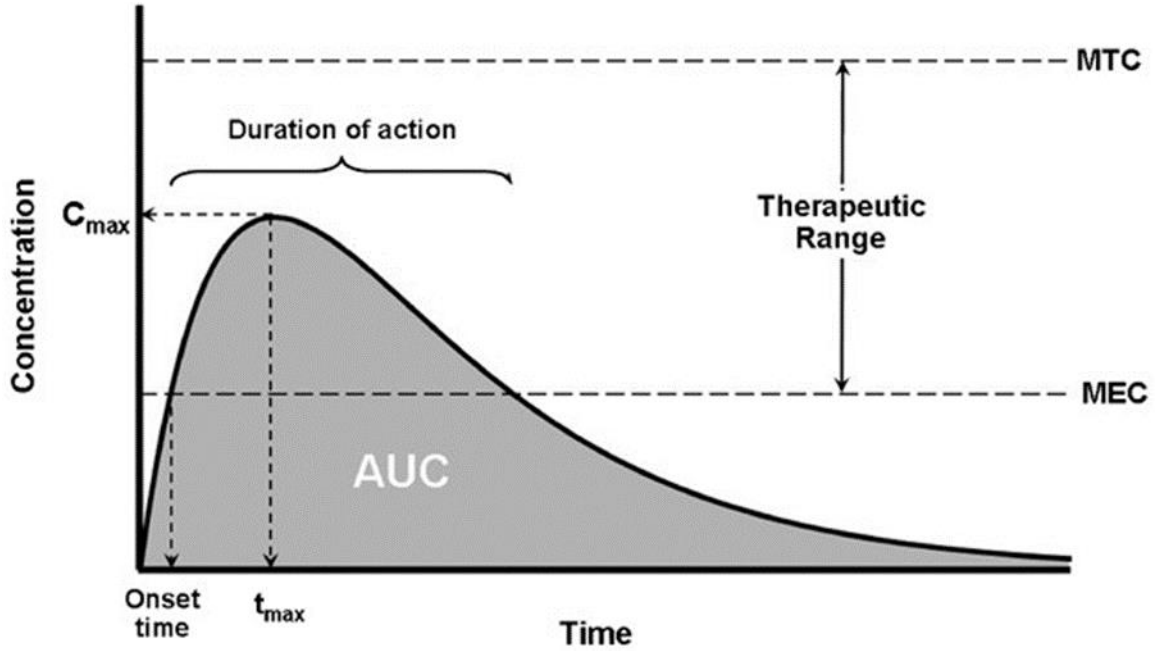
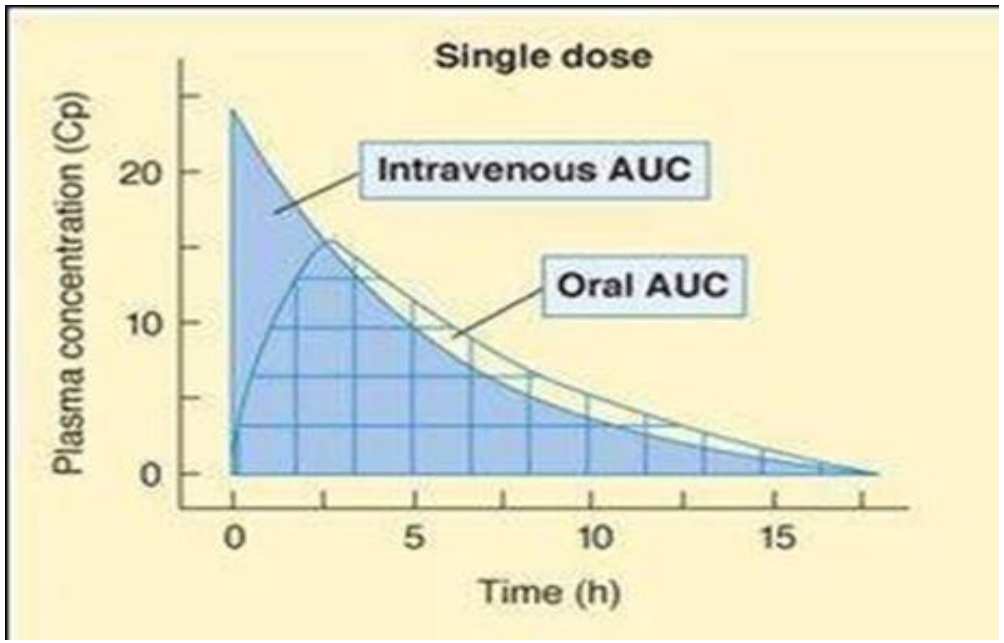


Figure 2: Area under the drug concentration curve

II-Bioavailability (BA or F): is the rate and extent to which an administered drug reaches the systemic circulation (the fraction of administered dose that reaches the systemic circulation. For example, if 100 mg of a drug is administered orally and 60 mg is absorbed unchanged, the bioavailability is 0.6 or 60%. It can be calculated using the following formula:

$$\textbf{Bioavailability} = \frac{AUC\ oral(route)}{AUC\ injected(IV)} \quad X\ 100$$



Where the AUC oral refers to the area under the blood concentration-time curve of orally administered drugs while the AUC injected represents the area under the blood concentration- time curve of intravenous (IV) injected drugs

Bioavailability of intravenous routes of administration 100

Other routes bioavailability reduced by incomplete absorption, first pass metabolism, that occurs before the drug enters the systemic circulation

III- Drug Concentration (C): is the amount of drug in a given volume of plasma. The usual unit is mg/L.

IV- Volume of Distribution (Vd): It is a pharmacokinetic parameter that represents the volume of fluid required to contain the total-body amount of drug homogeneously at a concentration equal to that in plasma (or blood).

$$V = \frac{\textit{Amount of drug in the body (A)}}{\textit{The plasma concentration of drug (C)}}$$

- Vd is low when a high percentage of a drug is bound to plasma proteins.
- Vd is high when high percentage of drug is being sequestered in tissues.

V- Clearance (CL): Clearance (CL) estimates the amount of drug cleared from the body per unit of time. Total CL is a composite estimate reflecting all mechanisms of drug elimination is calculated as follows:

The total body clearance = renal clearance + hepatic clearance + lung clearance etc..

VI- Elimination rate constant (Kel): The fraction of drug removed per unit of time and has unit of reciprocal time (h-1).

Kel= CL/Vd

VII- Elimination half-life (t1/2): It is the period of time required for the concentration or amount of drug in the body to be reduced by one-half. We usually consider the half- life of a drug in relation to the amount of the drug in plasma.

$T_{1/2}=0.693/Kel$

$$t\,½ = \frac{0.693 \times Vd}{CL}$$

- Drugs or substances that have a shorter half-life tend to act very quickly, but their effects wear off rapidly, meaning that they usually need to be taken several times a day to have the same effect.
- Drugs with a longer half-life may take longer to start working, but their effects persist for longer, and they may only need to be dosed once a day, once a week, once a month, or even less frequently.

From half-life estimate the duration of action for drug.

6x half-life =duration of action of the drug

- The majority of drugs follow what is called First-order kinetic, in which the rate of elimination is directly proportional to the serum drug concentration.
- Some few drugs are eliminated at a fixed rate, regardless of drug concentration. This is referred to as Zero-order kinetic.

First order

1. ↑Plasma drug concentration→ ↑rate of drug metabolism.
2. Rate of metabolism is proportional to drug concentration.
3. Constant proportion of drug eliminated per time.
4. Clearance constant.
5. Half-life is constant(time to metabolize 50% of drug)
6. Example :most drug at most doses.
7.

Time(hr)	Plasma conc.	Rate of elimin.
0	8 mg/l	4
1	4	2
2	2	1
3	1	0.5

Zero order

1. ↑plasma drug concentration →no↑ rate of metabolism.
2. Rate of metabolism becomes independent of drug concentration. Rate of drug metabolism constant.
3. constant amount of the drug eliminated per time.
4. clearance not constant.
5. half-life not constant.
6. Aspirin,Phenytoin.
7.

Time(hr)	Plasma conc.	Rate of elimin.
0	8	2 mg/l/hr
1	6	2
2	4	2
3	2	2

What is the steady State (SS)?

Rate of drug absorption = Rate of drug elimination.

(figure 3)Reached in 4-5 half-lives.

5 half-lives are required to eliminate drug from the body.

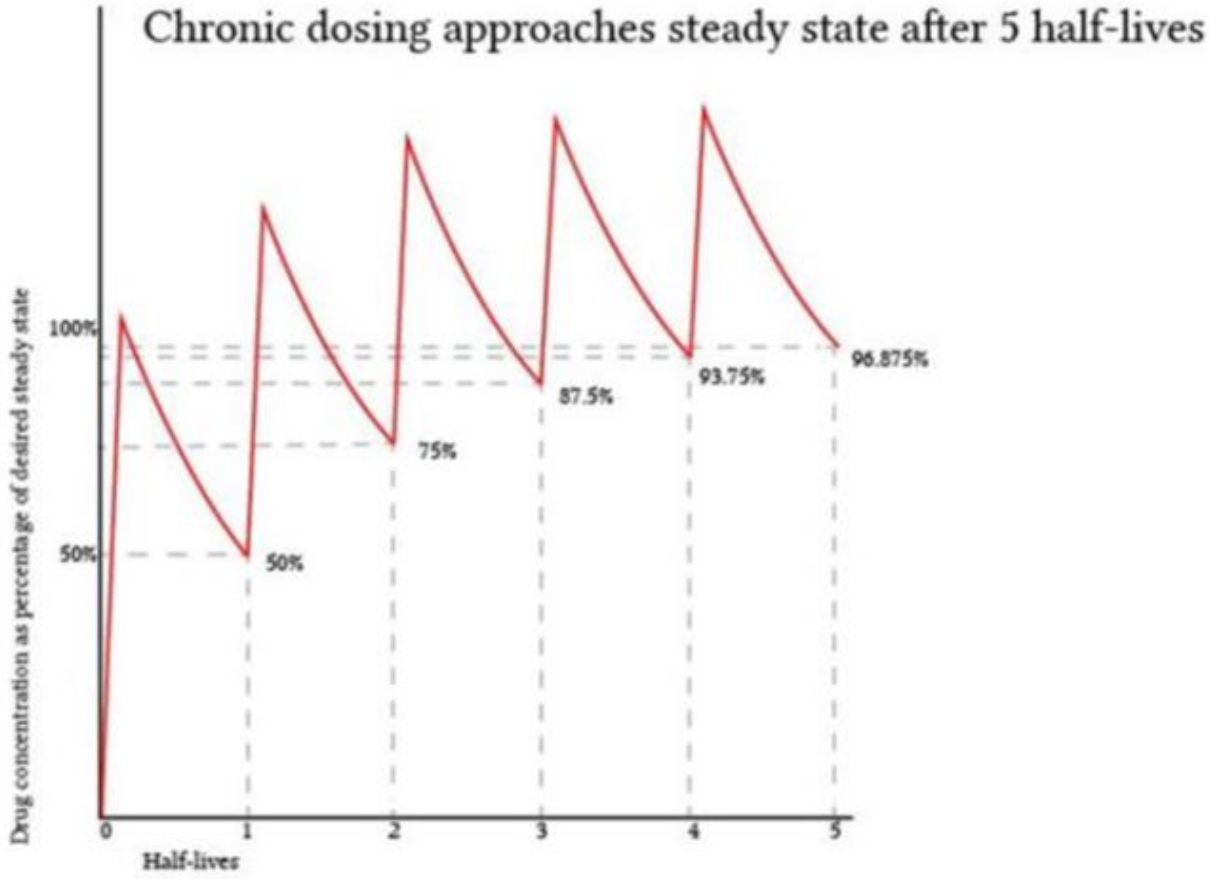


figure 3: study state concentration

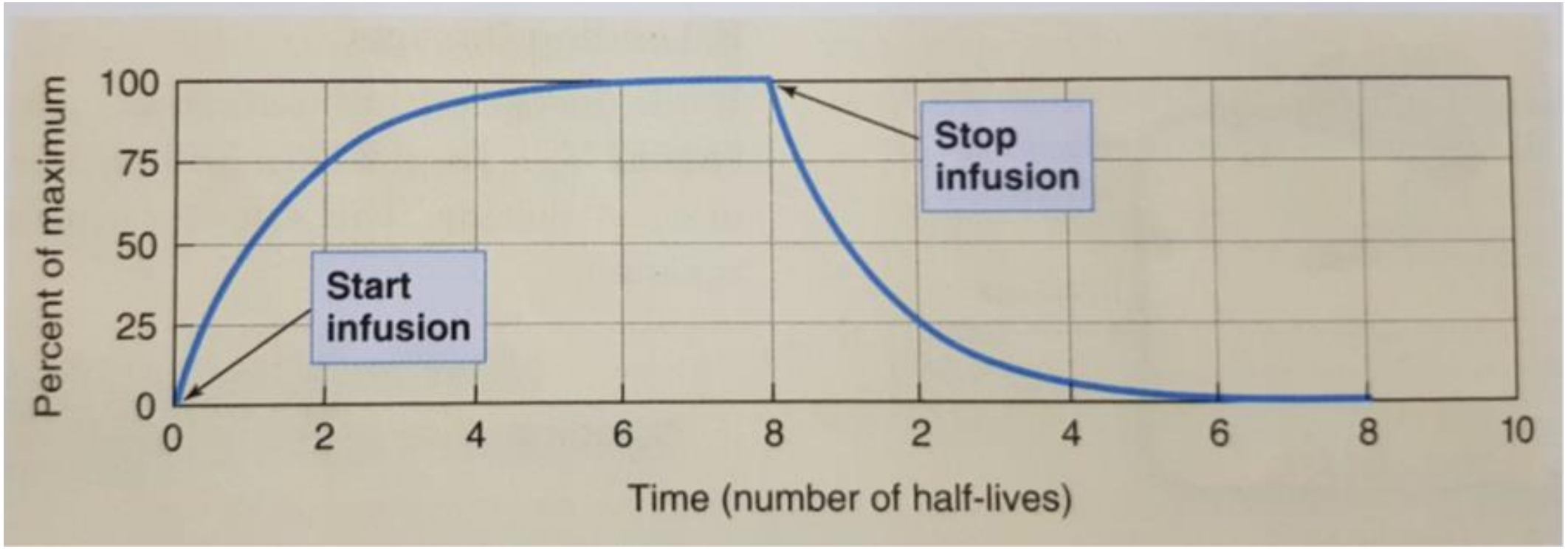


Fig: plasma conc ..(plotted as percent of maximum)of a drug (t 1/2 =1 hr) given by constant intravenous infusion for 8 half lives and then stopped the conc Rises smoothly with time and always reaches 50 of steady state after 1 half life, 75 after 2 half lives, 87 5 after 3 half lives, and so on The decline in conc After stopping drug administration follows the same type of curve 50 is left after 1 half life, 25 after 2 half lives and so on this approach to steady state on both increasing and decreasing limbs of the curve is characteristic of drugs that have first order kinetics

- If a drug initial concentration was 100 mg/mL in plasma, after the first t1/2 it will be 50 mg/mL, after the second 25 mg/mL, the third t1/2 12.5 mg/mL, the forth t1/2 6.25 mg/mL, the fifth t1/2 3.125 mg/mL.
- If the t1/2 was 2 hours, then we need (2*5) 10 hours to achieve steady state level and 10 hours to eliminate drug from the body.

Pharmacodynamics

Pharmacodynamics describe as the actions of a drug on the body.

The effect of the drugs can be one of the following:

1. Stimulatory: Some drugs act by increasing the activity of specialized cells, e.g. adrenaline stimulates the heart resulting in an increase in heart rate and force of contraction.

2. Depressive: Some drugs act by decreasing the activity of specialized cells, e.g. alcohol, barbiturates, general anesthetics, etc. depress the central nervous system,

3. Irritant: Certain agents on topical application can cause irritation of the skin and adjacent tissues.

4. Replacement: When there is a deficiency of endogenous substances, they can be replaced by drugs, e.g. insulin in diabetes mellitus, thyroxine in cretinism and myxedema, etc.

5. Cytotoxic: Drugs are selectively toxic for the infecting organism/cancer cells, e.g. antibiotics/ anticancer drugs.

Drug with receptors mediated mechanisms

Cells have different types of receptors, each of which is specific for a particular ligand. The term “ligand” refers to a small molecule that binds to a site on a receptor protein and produces a unique response.

Drug + Receptor ↔ Drug-receptor complex — Biologic effect

The receptors may be divided into four families:

A) Ligand-gated ion channels,

B) G protein—coupled receptors,

C) Enzyme-linked receptors, and

D) Intracellular receptors

RECEPTOR TYPES

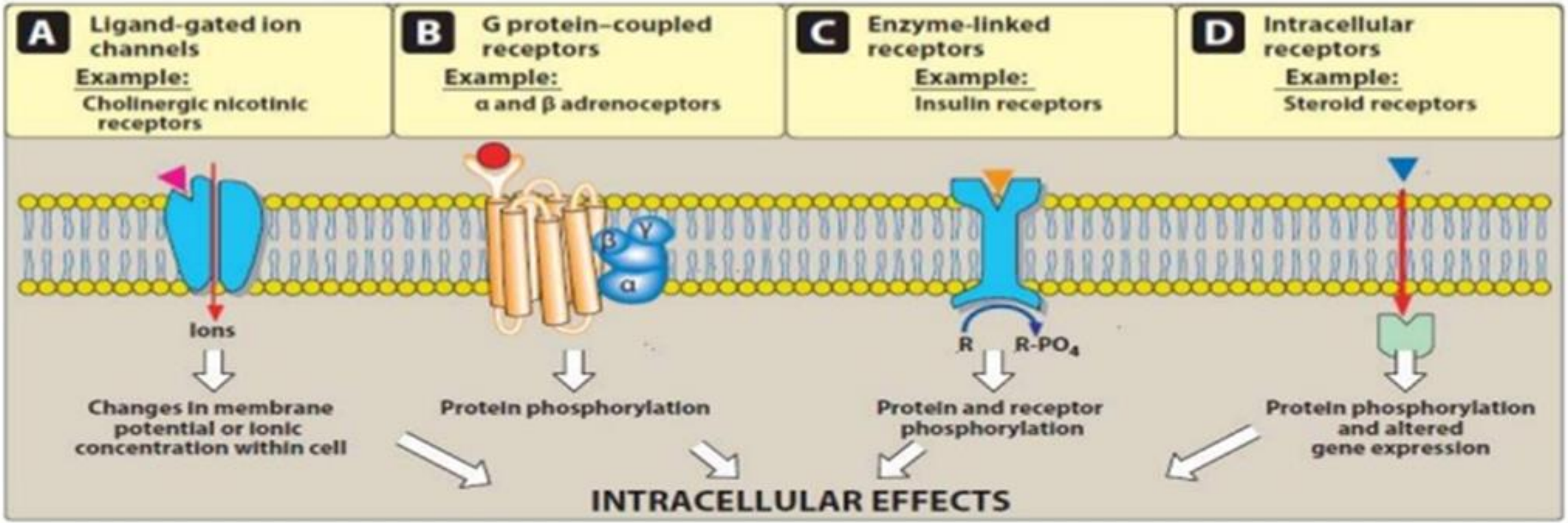


Figure 2.2

Transmembrane signaling mechanisms. **A.** Ligand binds to the extracellular domain of a ligand-gated channel. **B.** Ligand binds to a domain of a transmembrane receptor, which is coupled to a G protein. **C.** Ligand binds to the extracellular domain of a receptor that activates a kinase enzyme. **D.** Lipid-soluble ligand diffuses across the membrane to interact with its intracellular receptor. R = inactive protein.

According to the intrinsic activity of the drugs, they are classified into agonist and antagonist drugs.

An agonist drug can be defined as a chemical that binds to and activates the receptor to produce a biological response. Agonist drugs has been sub-classified into:

1.Full agonist: If a drug binds to a receptor and produces a maximal biologic response that mimics the response to the endogenous ligand, it is a full agonist,

2.Partial agonists: drugs that bind to and activate a given receptor but have only Partial efficacy at the receptor relative to a full agonist.

3.Inverse agonist: is a ligand that binds to the same receptor-binding site as an agonist; however, it produces an opposite effect by suppressing spontaneous receptor signalling (when present).

4.Agonists That Inhibit Their Binding Molecules: Some drugs mimic agonist drugs by inhibiting the molecules responsible for terminating the action of an endogenous agonist. For example, acetylcholinesterase inhibitors , by slowing the destruction of endogenous acetylcholine, cause cholinomimetic effects that closely resemble the actions of cholinoceptor agonist molecules even though cholinesterase inhibitors do not bind or only incidentally bind to cholinoceptors. Because they amplify the effects of physiologically released agonist ligands, their effects are sometimes more selective and less toxic than those of exogenous agonists.

The antagonists are type of receptor ligands or drugs that block a biological response by

binding to and blocking the receptors rather than activating them like an agonist. They are sometimes called blockers. Different types of antagonist drugs were recognised, which are:

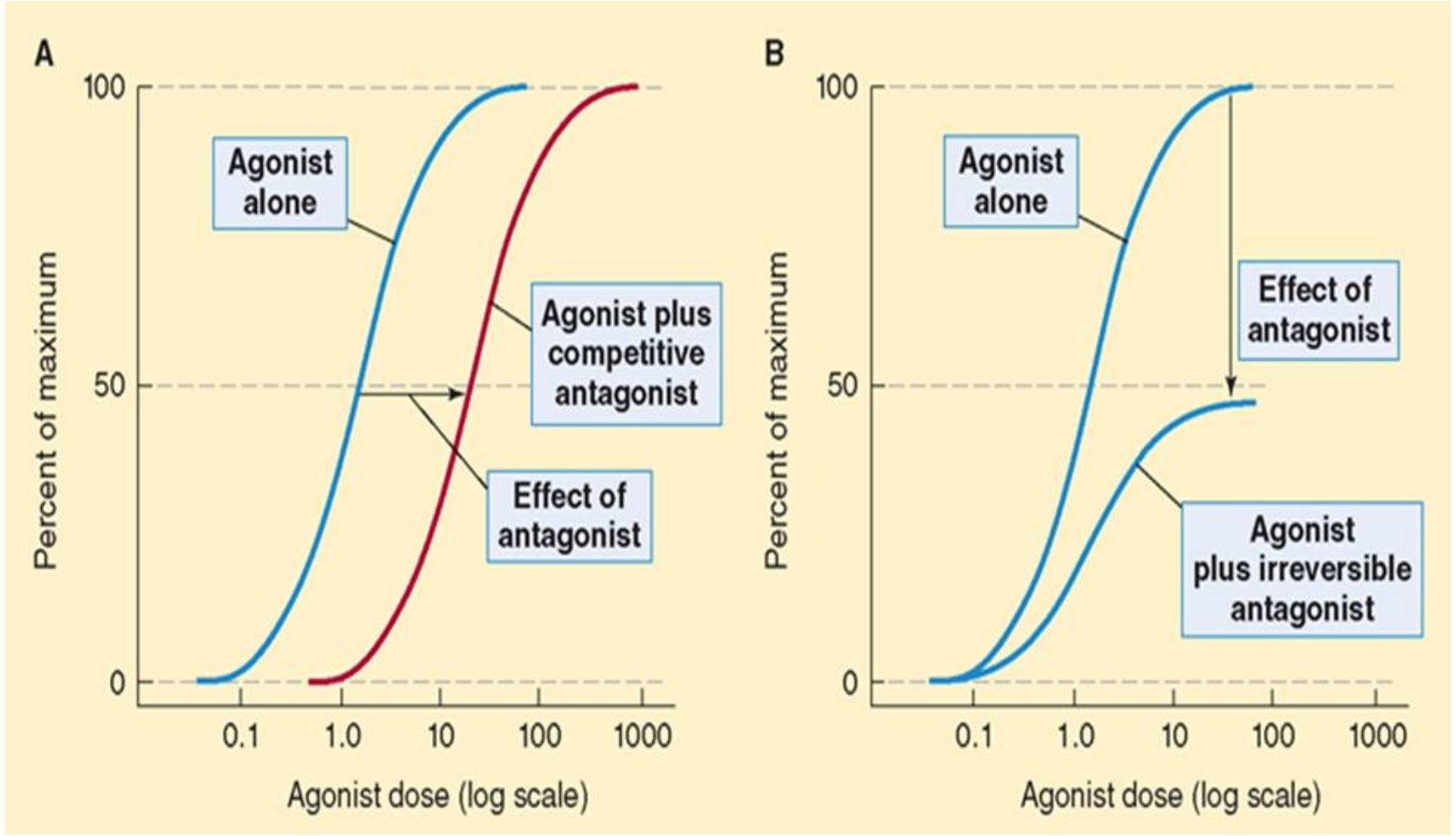
1. Pharmacological antagonism

- Competitive antagonists :competes with agonist in a reversible fashion for the same receptor site. the drugs that bind to receptors at the same binding site as the endogenous ligand or agonist, but without activating the receptor. Once bound, an antagonist will block agonist binding.
- The agonist when given in high enough concentration,can displace the antagonist and fully activate the receptor.
- Irreversible antagonists (**Non-competitive)** can be defined as the drugs that bind to the receptors or targets molecule in a manner which makes them impossible to reverse the binding (bind by covalent bond). No amount of agonist will overcome this sort of bond.

2.And finally, the functional antagonisms or physiological antagonism, which can be observed when an antagonist may act at a completely separate receptor, initiating effects that are functionally opposite those of the agonist. Take for example the glucocorticoids which increase the blood sugar while the insulin lowers it, but the two drugs act by completely different pathways.

3.Chemical antagonism**:** occurs when two drugs combine with one another to form an inactive compound. For example, interaction between heparin and protamine sulfate.

- A chemical antagonist interacts directly with the drug being antagonized to remove it or to prevent it from binding to its target.



Source: Trevor AJ, Katzung BG, Kruidering-Hall M, Masters SB: *Katzung & Trevor's Pharmacology: Examination & Board Review*, 10th Edition: www.accesspharmacy.com

Affinity: ability of drug to bind to its receptor, It is how well a drug and a receptor recognize each other.

Efficacy versus potency:

Efficacy: is the greatest effect -often called maximal efficacy- (Emax) of an agonist can produce if the dose is taken to the highest tolerated level. Efficacy is determined mainly by the nature of the drug and the receptor and its associated effector system. It can be measured with a graded dose-response curve,

- partial agonists have lower maximal efficacy than full agonists.

In(Fig.2.11) Drug A and B have equal efficacy (same Emax), Drug X has greater efficacy than drug Y.

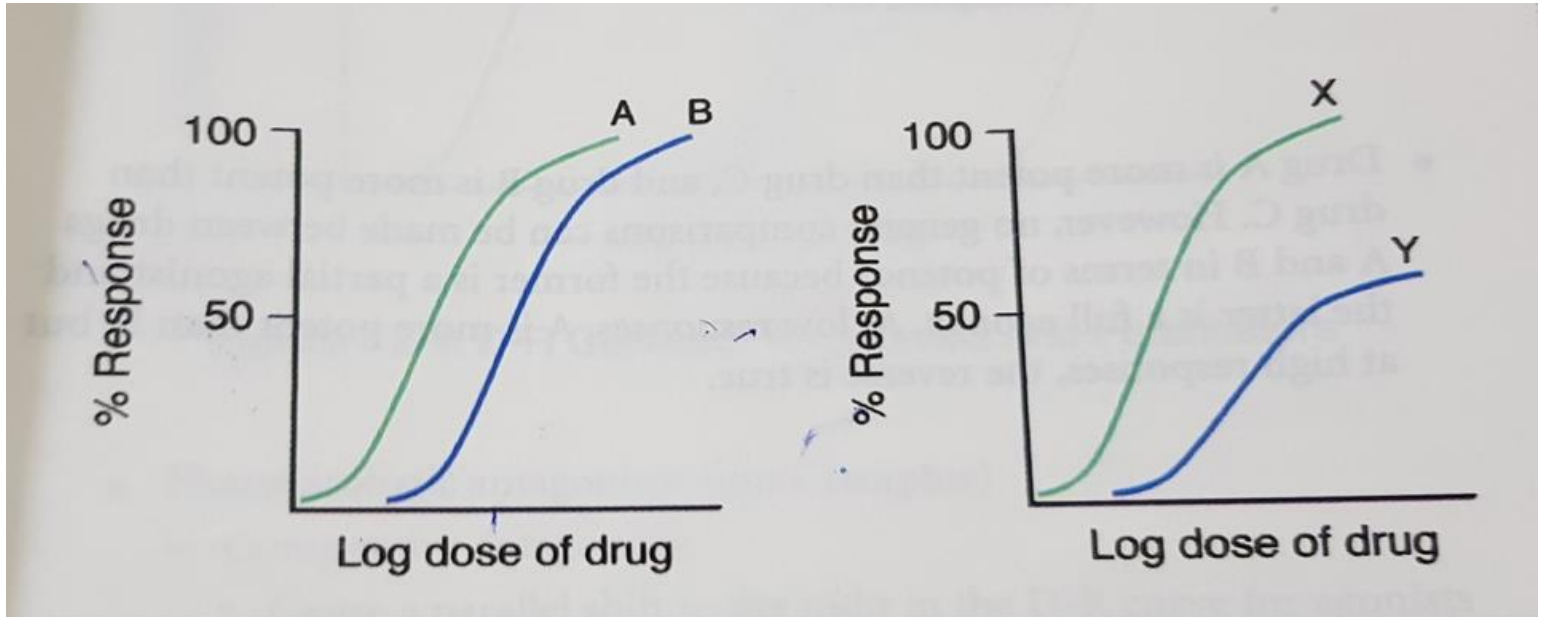


Fig.2.11:

Potency: the amount of drug needed to produce a specific effect.

• Potency is independent of efficacy and efficacy is usually more important than potency in selecting drugs for clinical use.
• In Fig. (2.11), Drug A is more potent than B because of the dose of drug B must be larger than dose of drug A to produce a given effect., X is more potent than Y.
•In Fig.2.12 Drug A and B have some efficacy but differ in potency

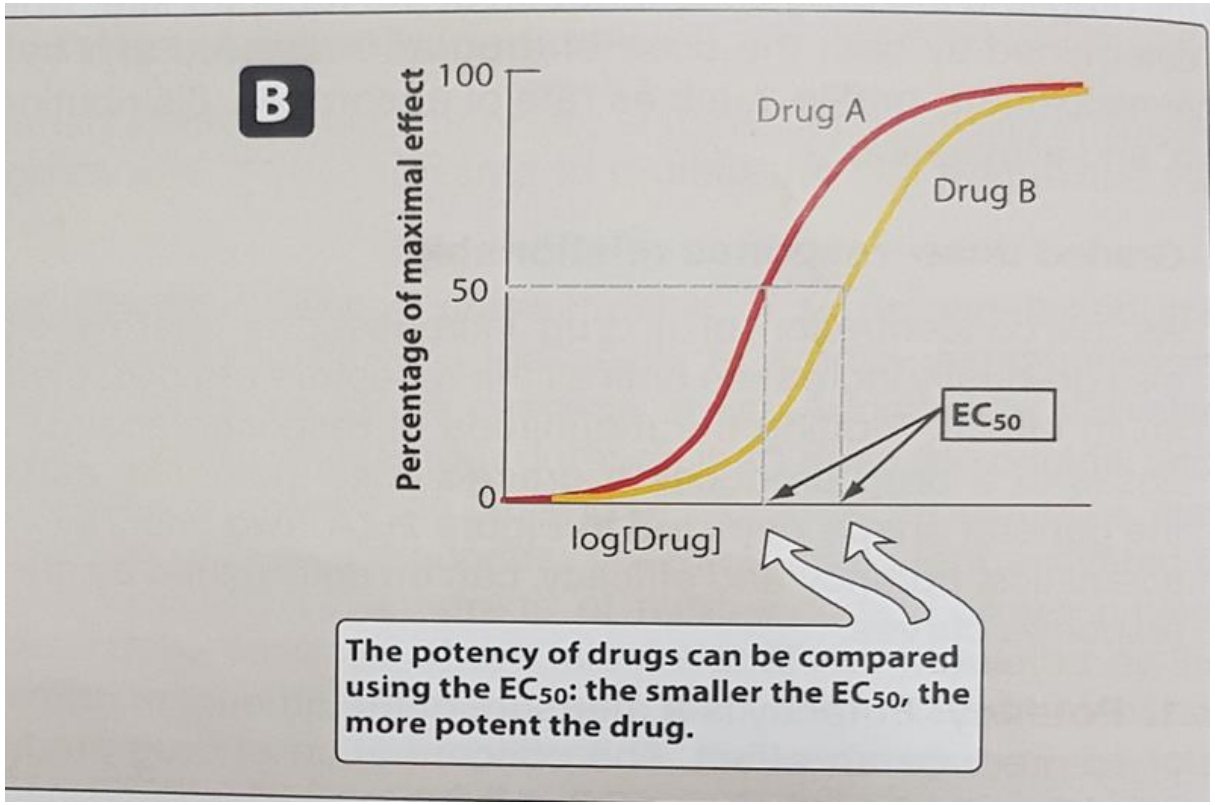
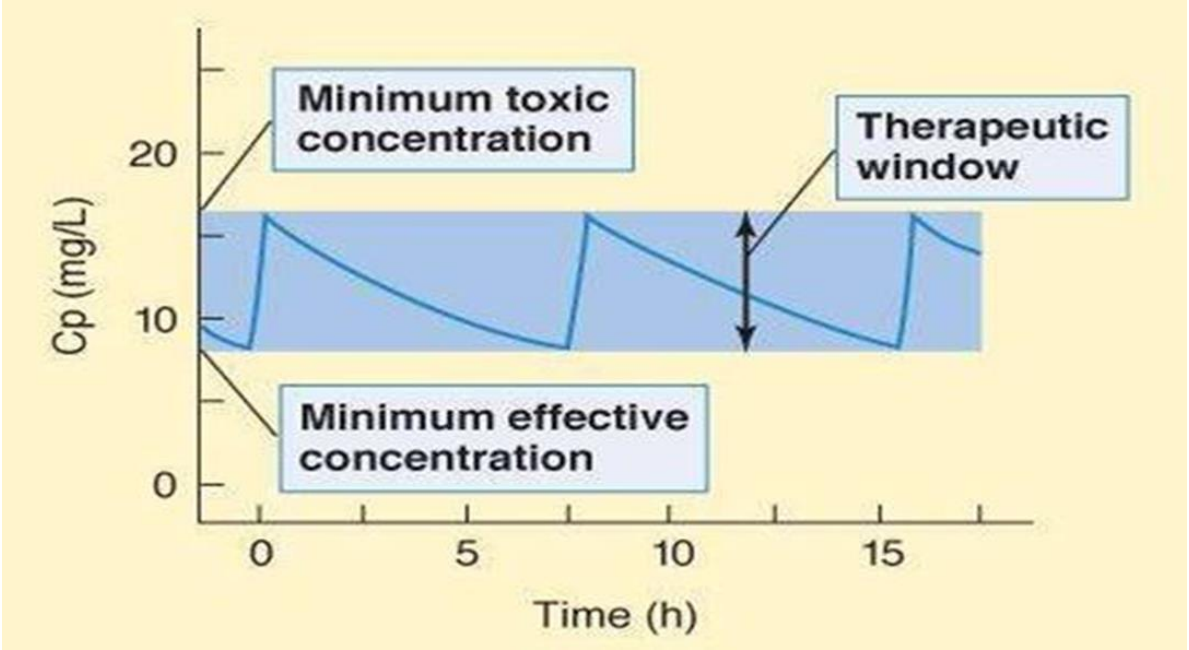


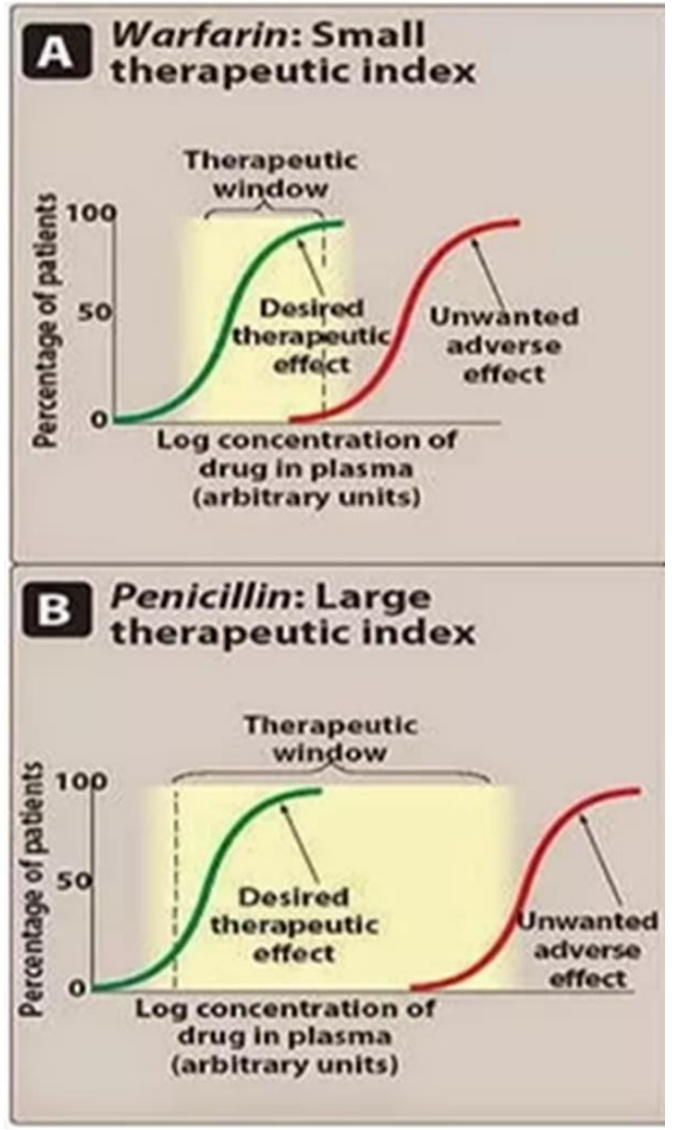
Fig.2.12

- **Therapeutic window:** is the safe range between the minimum therapeutic concentration and the minimum toxic concentration of a drug. These data are used to determine the acceptable range of plasma levels when designing a dosing regimen. e.g. therapeutic plasma conc. of theophylline 8 mg/L and toxic effect observed at 18 mg/L, Therapeutic window 8-18 mg/L. Fig.1-5



Therapeutic index: The concept of therapeutic index aims to provide a measure of the margin of safety of a drug, by drawing attention to the relationship between the effective and toxic doses

It is a ratio of the dose that produces toxicity in 50% of population (TD50) to the dose that produces a clinically effective response (ED50) in 50% of population



Enhancement of drug effects:

a) Additive drug effects: occur if two drugs with same effects, when given together, produce an effect that is equal in magnitude to the sum of the effects when the drugs are given individually. 1+1=2

b) Synergism: occurs if two drugs with same effect when given together, produce an effect that is greater in magnitude than the sum of the effects when the drugs are given individually. 1+1>2

c) Potentiation: occurs if a drug lacking an effect of its own increases the effect of a second active drug. 0+1>1