

Inverse agonist: drug that produces **effects** which are opposite to those of the agonist, e.g. β – **carbolines** bind to benzodiazepine receptor leading to stimulation and anxiety (opposite to benzodiazepines).

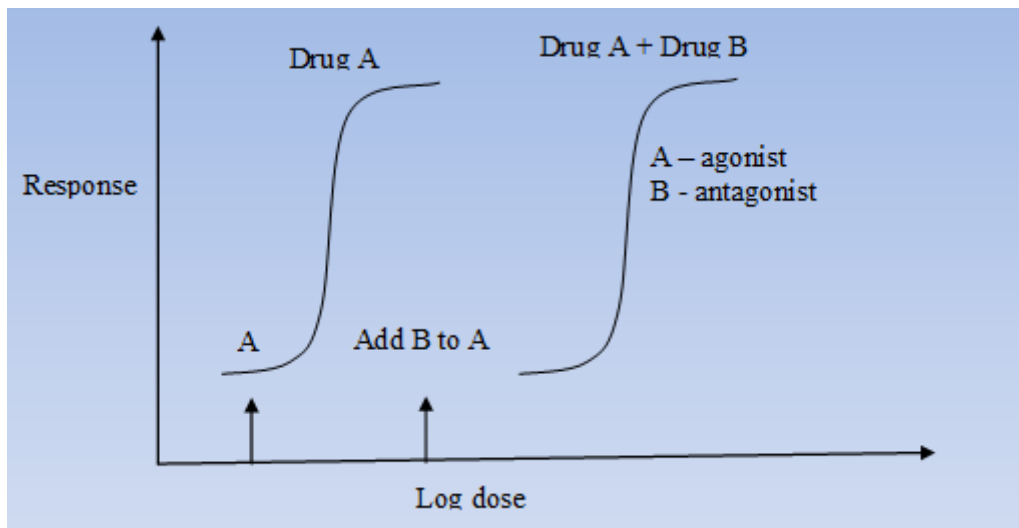
Competitive antagonism:

-If both agonist and antagonist bind to the same site on the receptor ,they are said to be competitive e.g.prazosin and noradrenaline at alpha- 1 receptors.

- Reversible binding between drug & receptors through hydrogen or electrostatic bonds,

-agonist and antagonist compete to occupy the receptor according to the law of mass action. The agonist is said to be surmountable.

-In the presence of an antagonist, higher doses of the agonist can produce a parallel DRC shifted to the right.



Non – competitive antagonism (concentration independent):

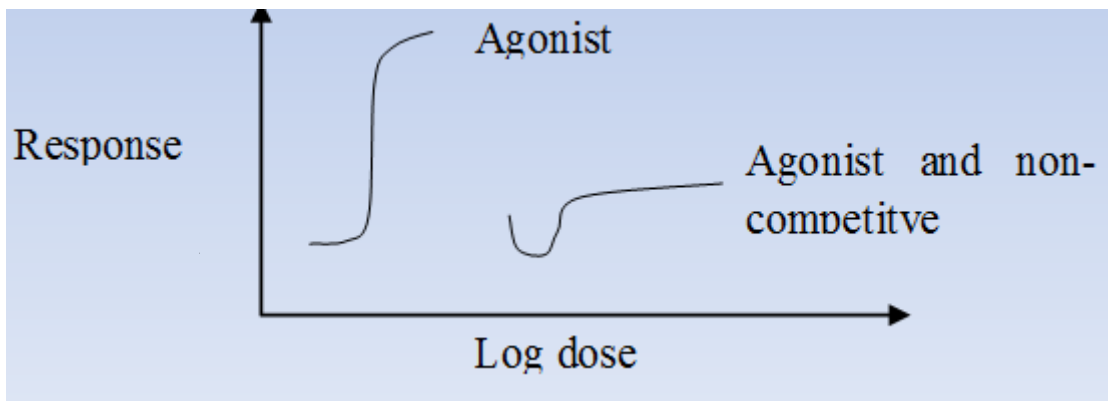
-If the antagonist binds to a site other than where the agonist binds ,the interaction is non-competitive or allosteric. Drug binds to the receptor through strong (covalent) bonds effectively, leading to irreversible binding

When antagonist occupy the receptor, increasing the agonist does not fully restore the response (insurmountable antagonism), restoration of response requires elimination of drug from the body, and synthesis of new receptors.

e.g.phenoxybenzamine at alpha receptor

❖ **Antagonism can occur in several ways:**

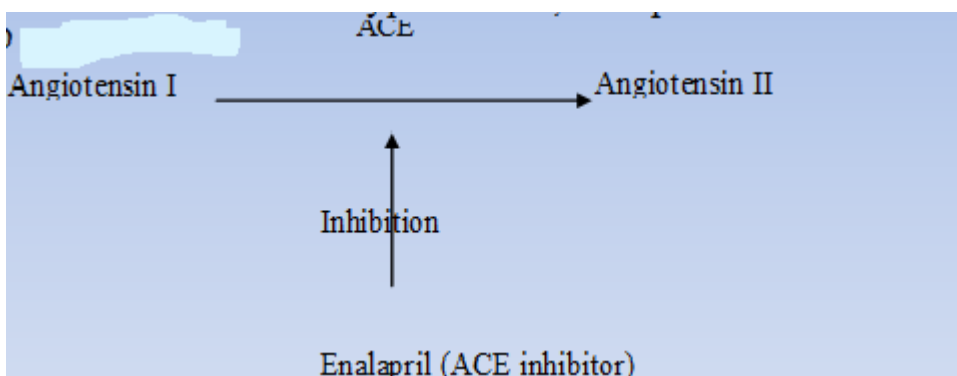
❖ **Pharmacological:** action of drugs on the same receptor, either competitive e.g.**propranolol + adrenaline on β -receptors**, or non – competitive e.g. **noradrenaline + phenoxy benzamine on α – receptor**.



- ❖ **Physiological (functional):** pharmacological effect of a drug is overcome by a second drug by different physiological mechanism, e.g. bronchoconstriction by **histamine (H₁ receptor)** can be antagonized by **adrenaline** through β_2 – receptor effect. Propranolol \downarrow heart rate by blocking β_1 receptors, while atropine \uparrow heart rate by blocking vagal activity.
- ❖ **Chemical:** antagonism by direct chemical interaction e.g. **antacids + gastric HCl**.

Enzymes: drugs may alter enzyme activity because they resemble a natural substrate and hence compete with it for enzyme.

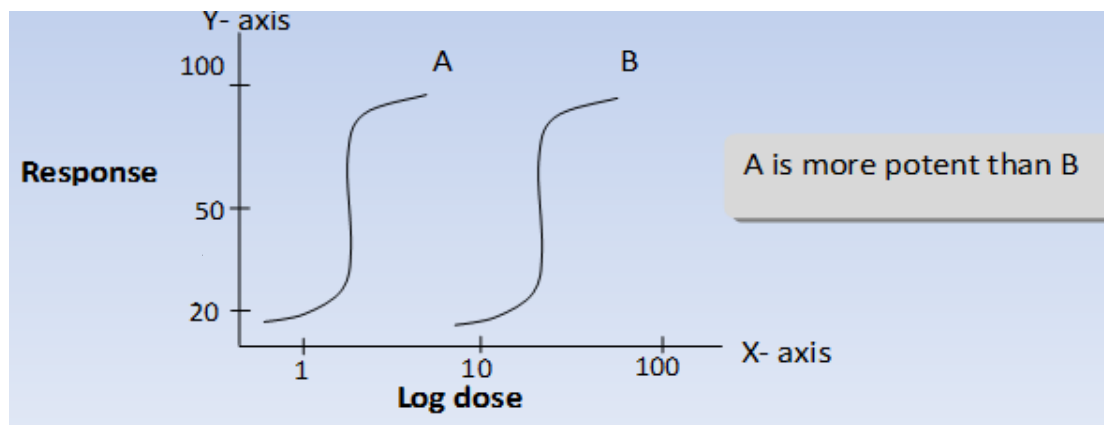
Competitive – reversible – enzyme inhibitors e.g. ACE inhibitors used in Rx of heart failure and hypertension, enalapril structure is similar to angiotensin I.



Non – competitive (irreversible enzyme inhibitors): e.g. organophosphorous insecticides, combine with Ach – esterase covalently, recovery of the enzyme activity requires new enzyme formation.

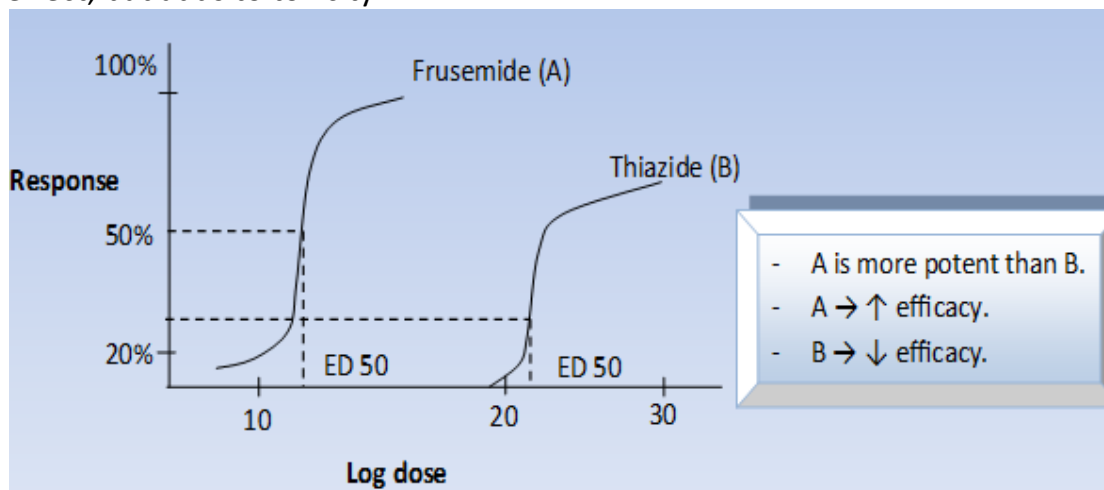
Dose – response curve (D. R. C.)

Drug response is proportional to its concentration at receptor sites which depends on the dose given and the pharmacokinetic parameters. \uparrow the dose will result in proportional \uparrow in response. When the dose and response plotted on a semi – log paper a sigmoid (S – shaped) DRC will result. The log concentration or dose is plotted on the horizontal X – axis and the response is plotted on the vertical Y – axis.



Steep rising and prolonged curve indicates that a small change in the dose → a large change in effect of that drug e.g. **Furosemide** diuretic.

For thiazide diuretics the curve soon reaches plateau, increasing the dose adds no diuretic effect, but adds to toxicity.



From graded DRC we can estimate:

- ❖ **Potency:** is the amount or dose of a drug producing a response of a given magnitude, the concentration producing an effect that is fifty percent of the maximum is used to determine potency (EC₅₀). The smaller the amount, more potent drug is.
e.g. 1 mg bumetanide gives diuretic effect = 50 mg of Furosemide diuretic effect, therefore, bumetanide is > potent than Furosemide.
- ❖ **Efficacy (intrinsic activity):** A maximum response induced by agonist. (E_{max}).
 - Efficacy depends on the number of drug – receptor complexes formed. If the drug binds to the receptors and produces no response so called **zero efficacy e.g. antagonist**
 - Drug + Receptor → (affinity) D.R. complexes (efficacy) Response →
 - **Amiloride** diuretic causes 5% excretion of Na⁺ load (**low efficacy**).
 - **Furosemide** causes 25% excretion of filtered Na⁺ (**high efficacy**).
 - Efficacy is more important than potency because a more potent drug may not reach its receptors in sufficient concentration due to some pathological condition.

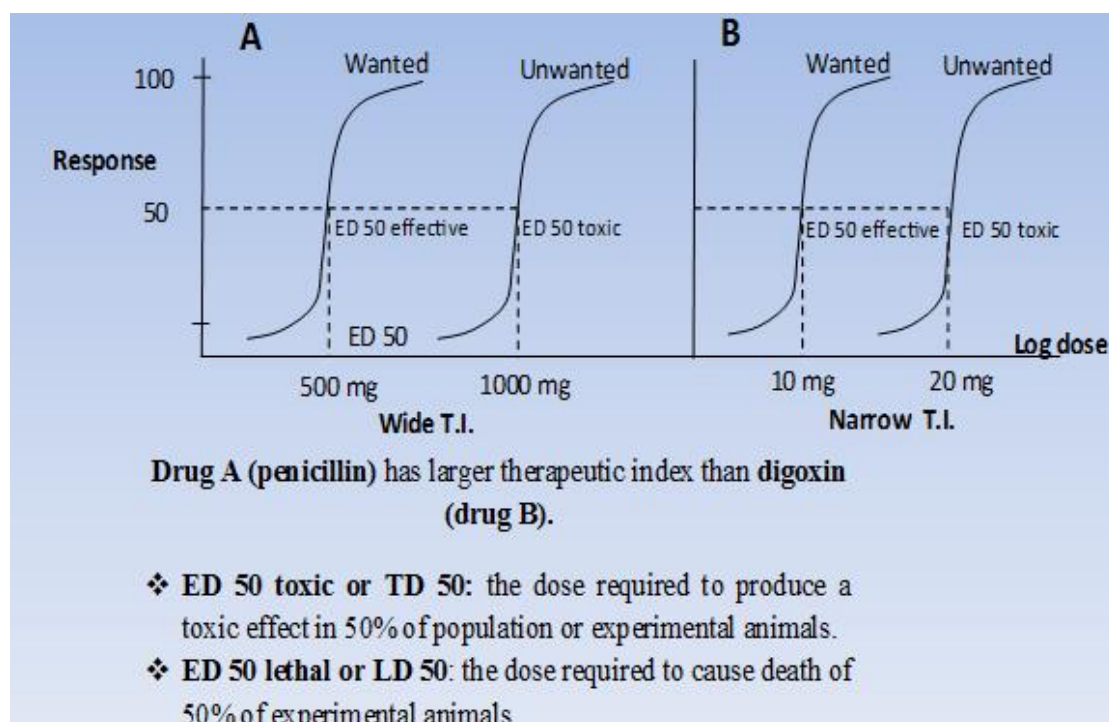
❖ Therapeutic index (T.I.):

Is the ratio between the dose that produces unwanted or **toxic** effect in 50% of patients to the dose that produces **therapeutic** effect in 50% of patients.

$$\text{Therapeutic index} = \frac{\text{Toxic dose (ED 50 - toxic)}}{\text{Therapeutic dose (ED 50 - effective)}}$$

T.I. is a measure of drugs safety. A large value indicates a wide margin between toxic and effective (therapeutic) doses i.e. safe drug. While small or narrow T.I. means that the difference between the toxic and therapeutic doses is small and such drugs need careful monitoring e.g. digoxin, lithium, phenytoin.

$$\text{T.I. may also estimated as } \frac{\text{LD 50}}{\text{ED 50}} \text{ (LD = lethal dose in 50\% of animals).}$$



Tolerance:

Is the gradual reduction in response to drugs following continued drug administration. Higher doses are needed to produce the previous effect obtained with a smaller first dose. Tolerance may be due to:

1. Down regulation of receptors e.g. morphine.
2. Generation of free radicals e.g. GTN in Rx of angina.
3. ↑ Metabolism due to enzyme induction as with alcohol taken regularly.

Natural tolerance: due to inherited factors e.g. warfarin.

Cross – tolerance: occurs between drugs of similar structure e.g. benzodiazepines, alcohol, barbiturates, anesthetics, antibiotics.

Tachyphylaxic:

Is a rapid loss of efficacy or response due to frequent repeated administration, more rapid than tolerance. e.g. rapid loss of bronchodilator effect of ephedrine due to depletion of neurotransmitters.

