PHARMACOLOGY

Quantitative Aspects of Drugs

OBJECTIVES:

- Determine quantitative aspects of drug receptor binding.
- Recognize concentration binding curves.
- Identify dose response curves and the therapeutic utility of these curves.
- Classify different types of antagonism

PHARMACOLOGY
435

QUANTIFICATION OF DRUG ACTION

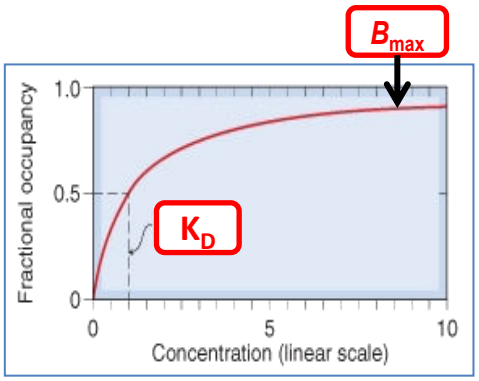
Concentration-Binding Curve	Dose Response Curve
Relate concentration [C] of Drug used (x- axis) to the binding capacity at receptors (y-axis)	Relate concentration [C] of Drug used (x-axis) to the response produced (y-axis)

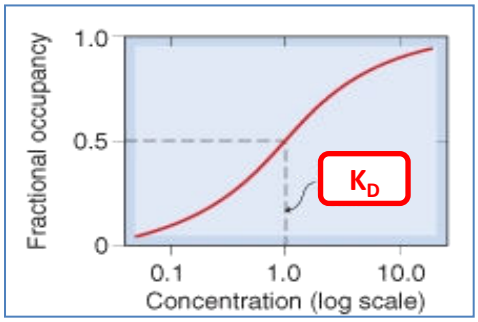
AFFINITY → **POTENCY** ← **EFFICACY**

Concentration-Binding Curve:

The relationship between drug binding & drug concentration is expressed mathematically by the following equation:

$$B = \frac{B_{max} \times C}{C + KD_{50}}$$





(B_{max}): Total density of receptors in the tissue

(k_D) = Concentration of Drug required to occupy 50% of receptors at equilibrium

QUANTIFICATION OF DRUG ACTION

Concentration-Binding curves are used to determine:

1. The binding capacity (B_{max}) → total density of receptors in the tissues.
2. The affinity of Drug for receptor (The higher the affinity of Drug for receptor the lower is the K_D) i.e. inverse relation
3. Classification of receptors to receptor subtypes
4. K_D (Concentration of Drug required to occupy 50% of receptors at equilibrium)

Dose-Response Curves:

How does response vary with Concentration?

A continuous response

↓Blood P, Heart Rate, FBG, Cholesterol,…

→ **GRADED DOSE RESPONSE CURVE**

An all-or-non response

prevention of convulsion, arrhythmias or death…..

→ **QUANTAL DOSE RESPONSE**

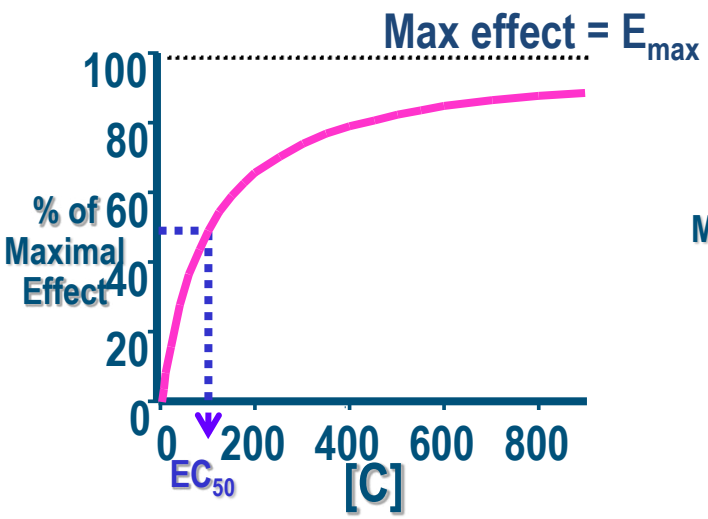
Relate C to % of patients eliciting the *:*

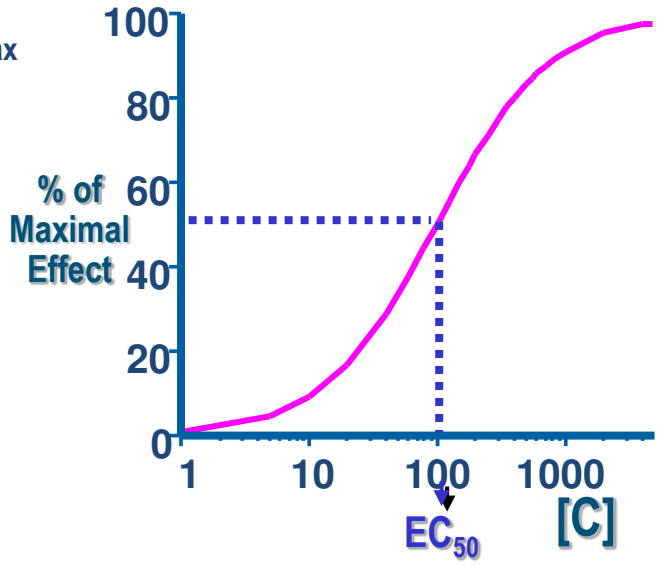
- specified therapeutic response
- adverse response
- lethal outcome

Dose-Response Curves

Features of Graded Dose-response Curve

1. Response is gradual
2. Gradual increase in response by increasing the dose (continuous response)
   .e.g. blood pressure, heart rate, blood glucose level, cholesterol,…
3. Curve is usually sigmoid in shape





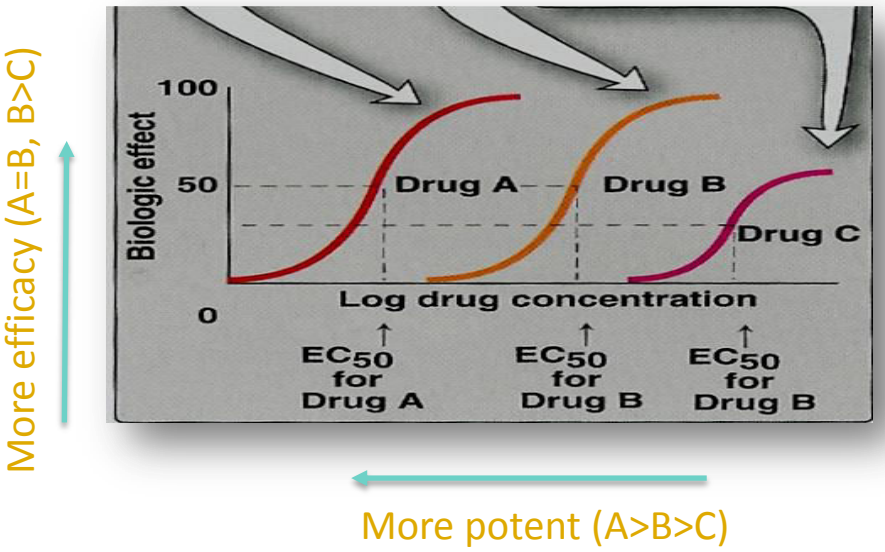
important note: As C ↑ → response ↑

Graded dose-response curves are used to determine:

1. **Max efficacy (E_{max})** : is the maximal biological response produced by a drug. Also, E max means all of the receptor are occupied (B max)
2. **Median effective concentration (EC50) :** is the concentration of the drug that gives 50% of (E max).
3. **Potency :** the concentration of drug required to produce a specified response **(**Compare the relative potency and efficacy of drugs that produce the same effect**)**.

Potency is inversely proportional to EC50.

Question: If we have three drugs A,B,C . EC50 for drug A = 10 , EC50 for drug B = 50 , EC50 for drug C = 100. Which one of them is more potent ?!
Answer: drug A
Why ? Because drug A produces the effect with small amount of concentration , and then will reduce the side effects.



Quantal Dose-Response Curves:

Features of Quantal Dose-response Curve:

1. Relate drug concentration to % percentage of patients responding **(all or none response)**.
2. The response may be: Therapeutic response, adverse effect or lethal effect.

Quantal dose-response curves are used to determine:

1. **Median Effective Dose (ED50) :** the dose of drug Required to exhibit a therapeutic effect in 50% of patients.
2. **Median Toxic Dose (TD50) :** the dose of drug required to exhibit a toxic effects in 50% of patients. (means the side effects)
3. **Median LETHAL Dose (LD50):** the dose of drug required to exhibit death in 50% of patients.

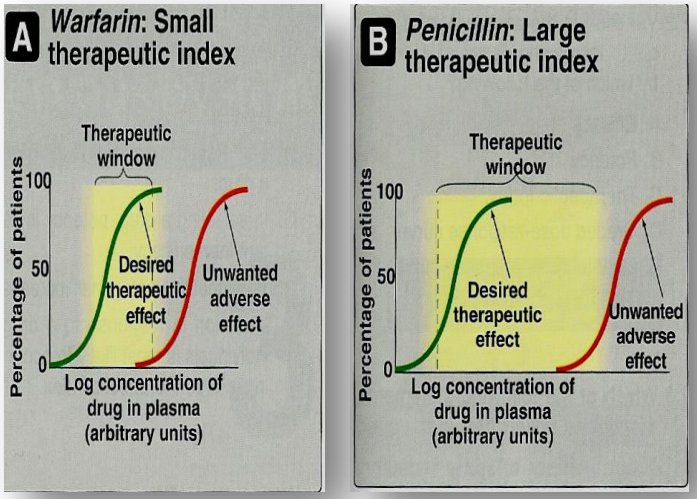
Quantal Dose-Response Curves:

4. **Therapeutic Index:** It is a measure of safety profile.

- Large value = Drug has a wide margin of safety. E.g. Diazepam

- Small Value = Drug has a narrow margin of safety. E.g. Digoxin

$$\text{Therapeutic Index} = \frac{TD50}{ED50}$$



Antagonism

DEFINITION: It is the decrease or the complete abolishment of the effect of one drug in the presence of another.

Types of Antagonism:

1. Chemical Antagonism
2. Physiological Antagonism
3. Pharmacokinetics
4. Pharmacodynamics (Receptor Blockage)
   - Competitive: -Reversible -Irreversible
   - Non-Competitive

Antagonism

1. Chemical Antagonism:

- Simple chemical reaction & loss of activity
- No receptor.
- E.g. Dimercaprol reduces heavy metal toxicity (as in lead toxicity).

2. Physiological Antagonism:

- Two drugs act on different receptors to produce different physiological effects.
- E.g. Adrenaline & Histamine
- Adrenaline is used in anaphylactic shock to reverse action of histamine.

Adrenaline → Vasoconstriction (↑ BP) & bronchodilation.

Histamine → vasodilatation (↓BP) & bronchoconstriction.

3. Pharmacokinetic Antagonism:

- The antagonist effectively reduces the concentration of the active drug at the site of action.
- e.g. Phenobarbitone accelerates hepatic metabolism of warfarin

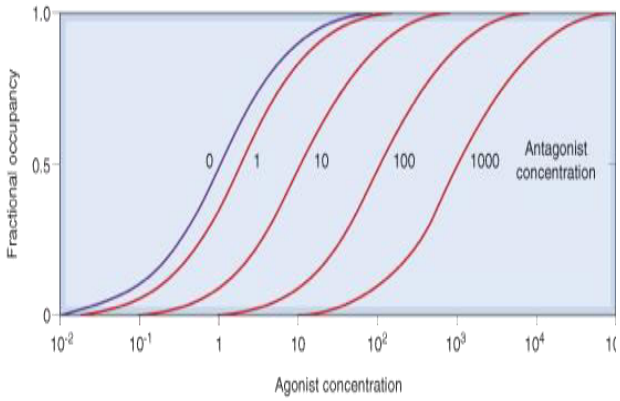
4. Pharmacodynamic Antagonism:

A) Competitive Reversible:

- Two drugs compete for the same receptor.
- The antagonist partially or completely prevents the pharmacological effect of agonist.
- Antagonist dissociate rapidly from receptor.
- Antagonism **can be overcome** by increasing the concentration of the agonist **(Surmountable).**
- Parallel shift of the curve to the right, without any change in slope or maximum
- E.g. acetylcholine and atropine.

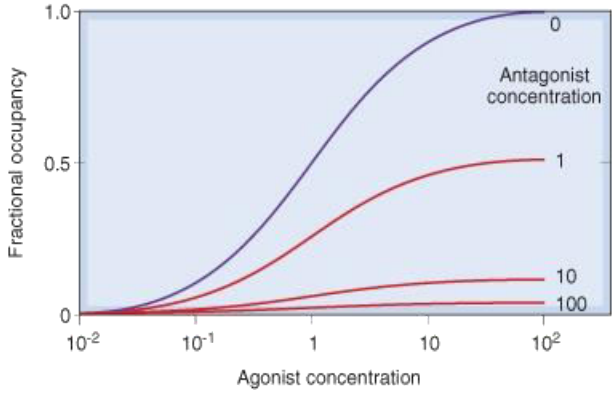
B) Competitive Non-Reversible:

- Two drugs compete for the same receptor.
- Antagonist forms stable, permanent/near permenant chemical bond with receptor.
- The original response **can not be overcome** even by increasing the dose of the agonist **(non-Surmountable).**
- No parallel shift
- a decrease in slope and a reduced maximum are obtained.
- e.g. phenoxybenzamine and noradrenaline.



Reversible

Parallel shift to the right, without any change in slope or maximum

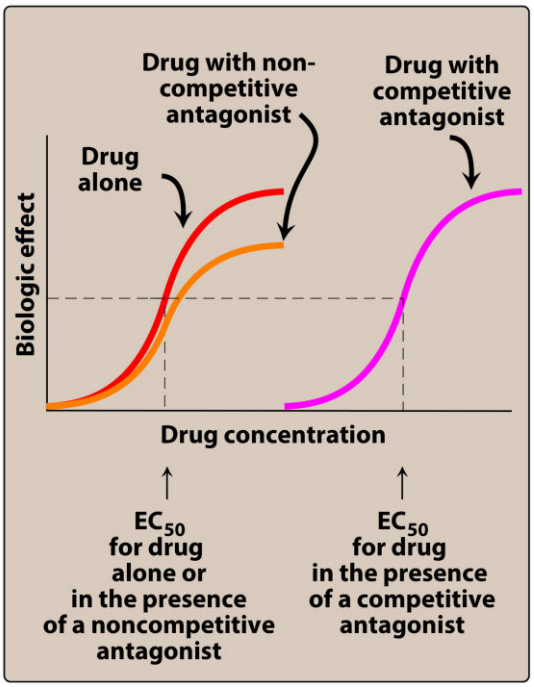


Irreversible

No parallel shift
But both a decrease in slope and a reduced maximum are obtained.

C) Non-Competitive:

- Antagonist block at some point the chain of events that stimulate the response of agonist.
- Agonist and Antagonist can be bound simultaneously.
- Antagonism **cannot be overcome** by increasing concentration of agonist **(non-Surmountable).**
- E.g. verapamil and noradrenaline.



THANK YOU FOR CHECKING OUR WORK

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PHARMACOLOGY
435