Quantitative Aspects of Drug Action

Lecture no. 6

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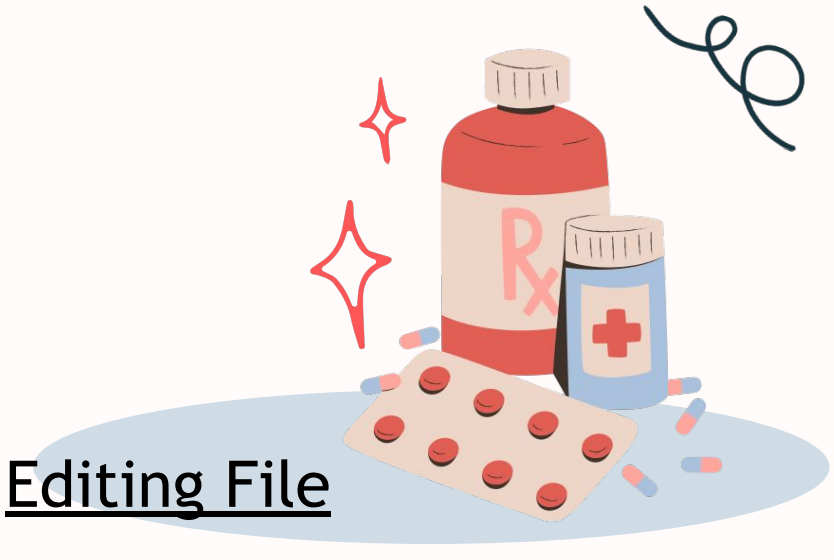

Editing File

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Objectives

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

Note: All the curves in this lecture are included the Exam.

POTENCY

The amount of drug needed to produce effect

Affinity

Ability of a drug to combine with the receptor.
OR
The capacity of a drug to form a complex with the receptor (DR complex).

Concentration-Binding Curve

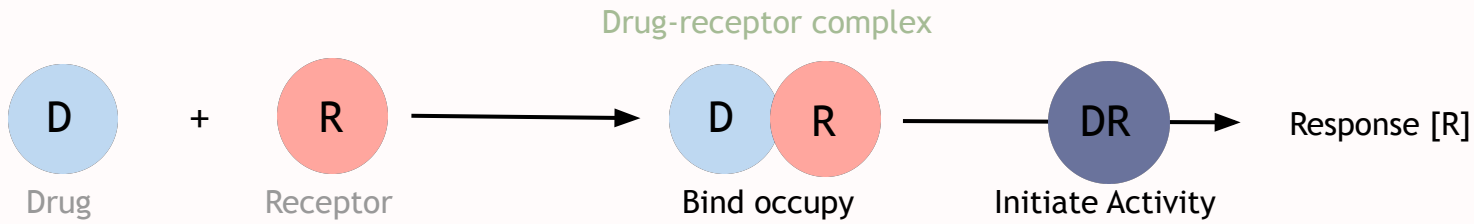
Efficacy
(intrinsic Activity)

Capacity of a **drug-receptor complex** (D-R) to produce an action.
OR
The ability of the drug once bound to the receptor to trigger a response.

Dose-Response Curves

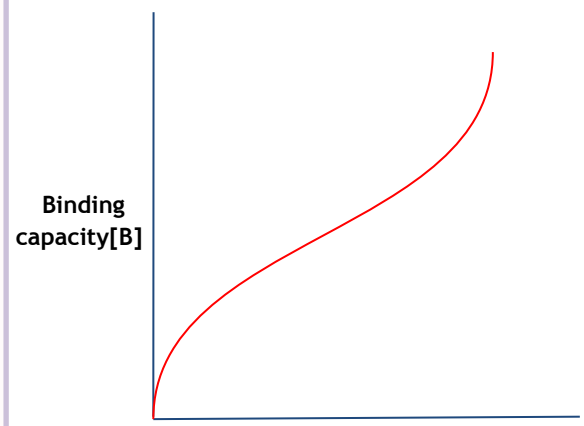
E max definition in slide 8

Quantify aspects of drug action



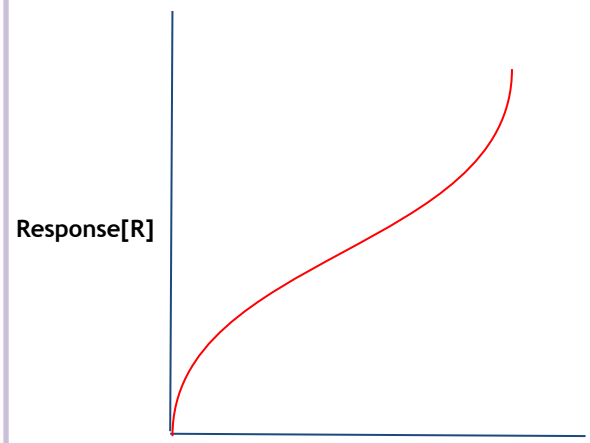
Affinity
Concentration-Binding Curve

Relate concentration **[C]** of D used (x-axis) to binding capacity **[B]** at receptors (y- axis).

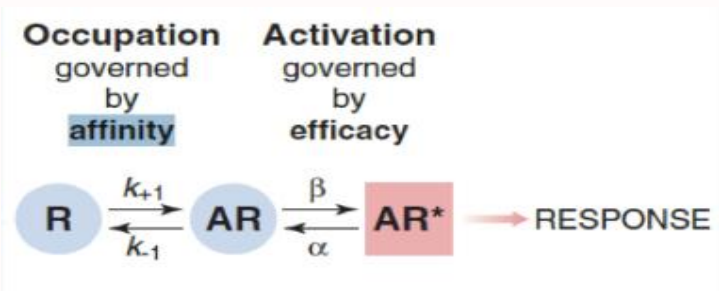


Efficacy
Dose-Response Curves

Relate concentration **[C]** of D used (x-axis) to response **[R]** produced (y- axis).



*Curves are only for explanation in this slide



Drug affinity and efficacy determine drug potency.

CONCENTRATION BINDING CURVES

- Is a correlation between **drug concentration [C]** used (x- axis) and **drug binding** capacity at receptors **[B]** (y-axis).

= is relation between concentration & drug binding
i.e. **Affinity**

Concentration-Binding curves are used to determine:

B max (the binding capacity)

The total density of receptors in the tissues. (saturation)

KD50

The concentration of the drug required to occupy 50% of receptors at equilibrium.

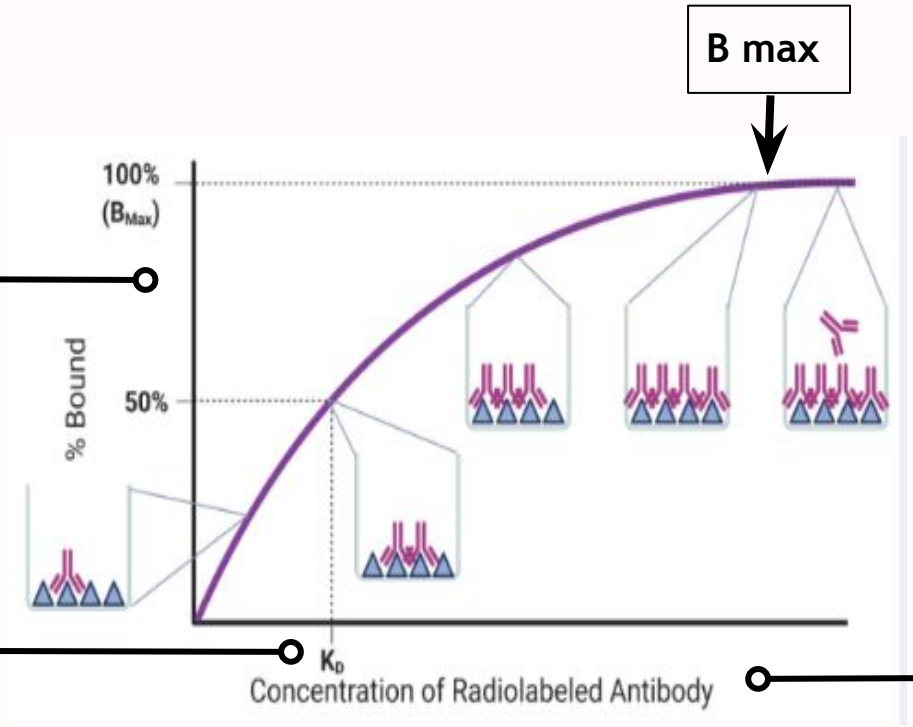
The affinity of drug for receptor

The higher the affinity of D for receptor, the lower is the KD i.e. inverse relation

- **(Binding Potential = $\frac{Bmax}{KD}$).**

CONCENTRATION BINDING CURVES

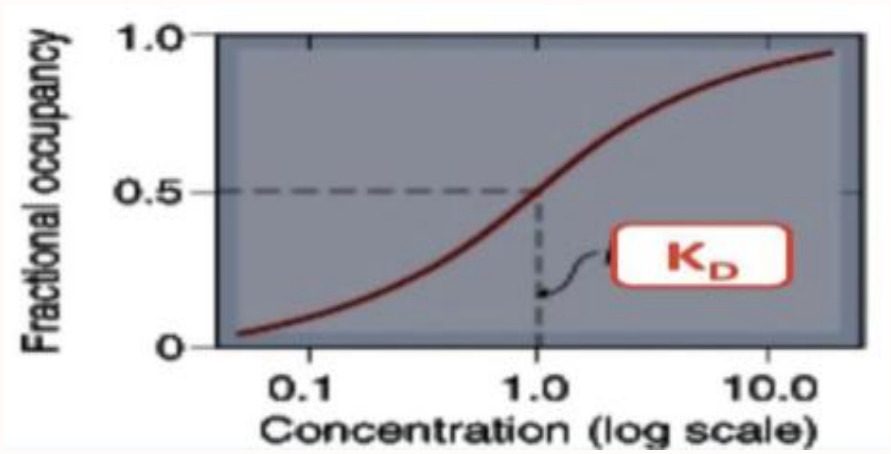
B max = Total density of receptors in the tissue
(Affinity) (all receptors are occupied(saturated))



The number of receptors that have been occupied by the drug = fractional occupancy.

The less KD the better for the patient because the affinity of the drug will be high which gives better effect.

The higher the concentration, the higher the drug binding is going to be.
Direct correlation until it reaches (B max) =when all receptors are full



(K_D) = [C] of D required to occupy 50% of receptors at equilibrium.

DOSE - RESPONSE CURVE

Concentration Effect

- a correlation between **drug concentration [D]** used (x- axis) and **drug response [R]** (y-axis).

Used to study:
- how response varies with the concentration of the drug or dose.
- relation between concentration & Response = Efficacy.

Types of Dose-Response curves

Graded Dose-Response Curve

- Example: diabetes patients drugs:

1st tablet -> blood glucose level decrease
(E.g: was 200 and became 180) .
2nd tablet - > the response increase
(blood glucose level keeps decreasing)
(E. g: was 180 and became 150)
3rd tablet -> reach the normal level.

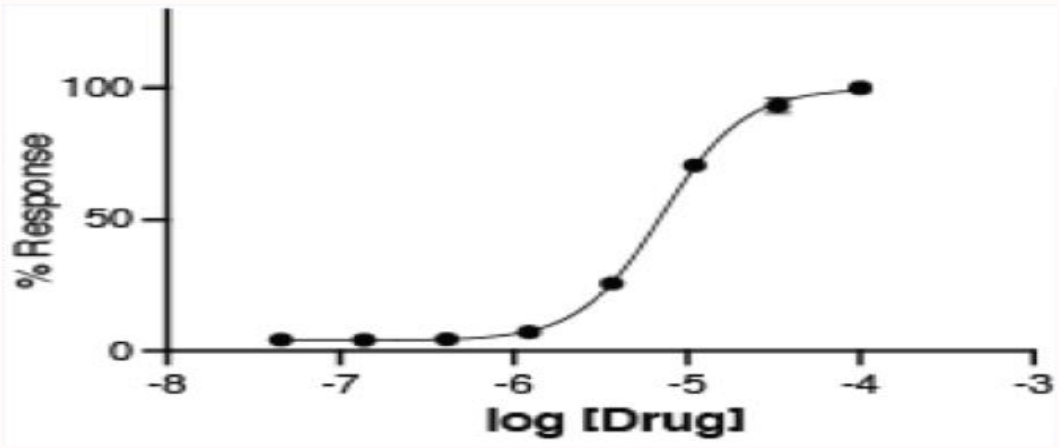
The response is gradual:
Increase the concentration -> the response increase.

Quantal Dose-Response Curve (all or none)

- Example : Epilepsy drugs* "ادوية الصرع":

Epilepsy has no grades only frequent seizures "نوبات الصرع" so it has to be a drug that gives the response at once (has no grade) either the drug gives response or not .

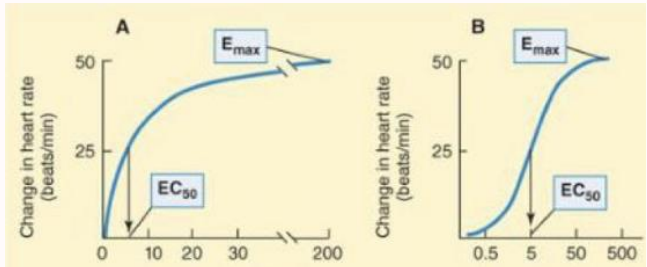
Another Example: Arrhythmia
Arrhythmia: Irregular heartbeat either too slow or too fast.



GRADED DOSE - RESPONSE CURVE

- Relates drug concentration to response.
- Response is gradual.
- Gradual increase in response by increasing the dose (continuous)
- e.g. Decrease blood pressure, heart rate, blood glucose level, cholesterol... (mostly with measurable quantities).
- Curve is usually sigmoid in shape (S shape) as it is plotted using log EC_{50}

Graded Dose-Response curves are used to determine:



Maximum Efficacy (E max):

-is the maximal biological response produced by a drug.
-The value of intrinsic activity ranges from 0 to 1

Median Effective concentration (EC50):

-is the concentration of the drug that produces a response to 50% of the maximal response (Emax)

Potency:

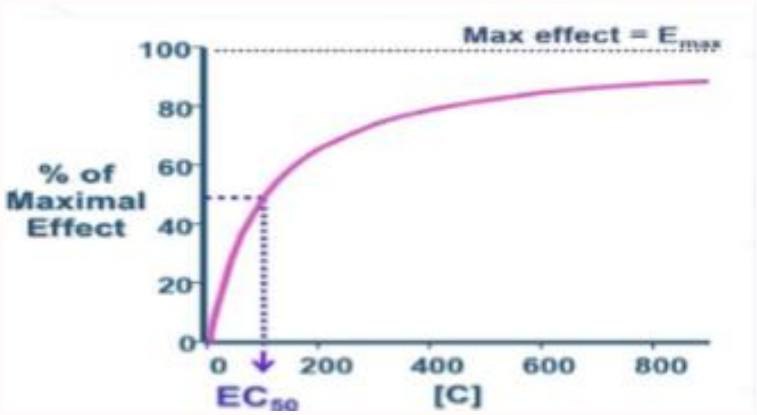
-the drug concentration required to a produce a specified response(50% of the maximal response = EC50).
-The Potency of drugs can be compared using EC50
-The smaller the EC50 the more potent the drug.
Potency is inversely proportional to EC50

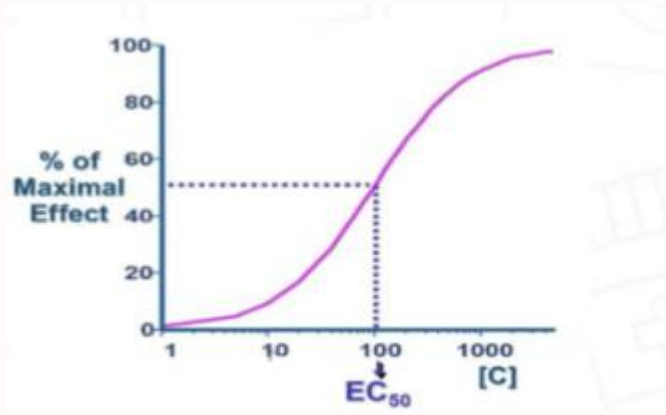
Efficacy: The higher efficiency of drugs at the Efficacy Maximum Effect. (Team 439)

GRADED DOSE - RESPONSE CURVE

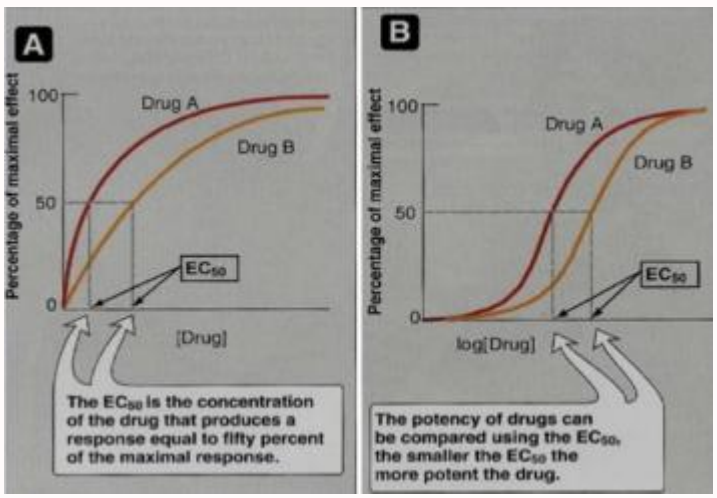
- **Emax**: Effect when all the receptors are occupied by D (efficacy response).
- **EC50**: that gives half the maximal effect.

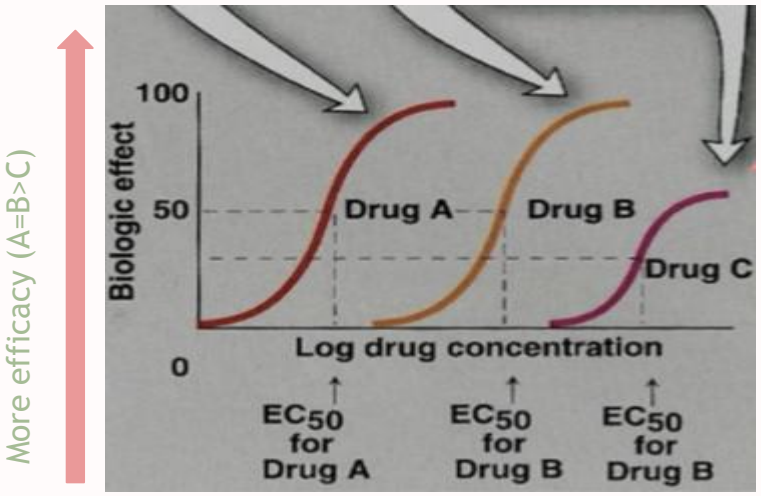
As C ⬆️ , Response ⬆️





- Both curves measures the dose & response but the S shaped one is the log of the dose (to make the measurements easier).





→ Drug A and B have the same efficacy but different potency and they have more efficacy than drug C.
A(most potent) > B > C (Least potent)

GRADED DOSE - RESPONSE CURVE

Team 443 note

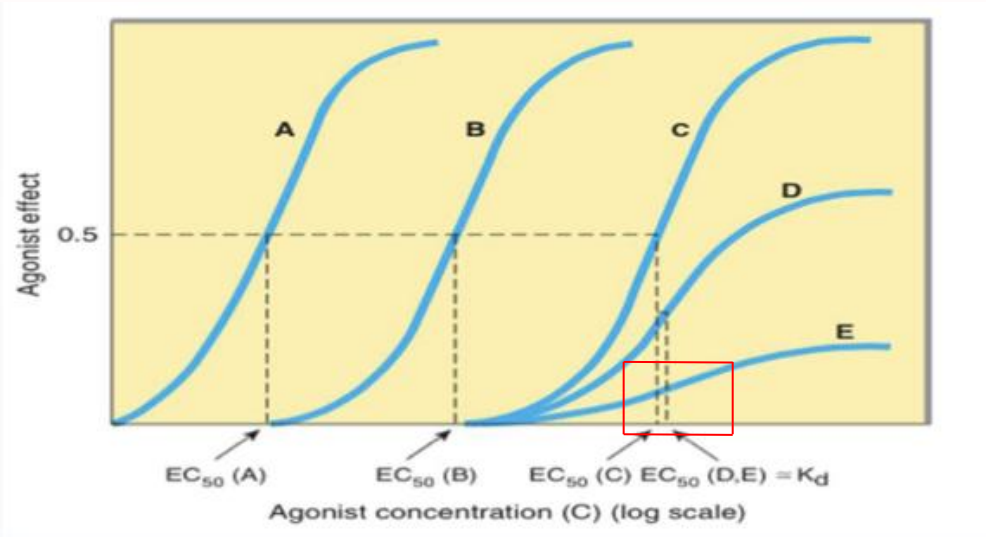
- **Which of the following curves represent the least potent drugs ?**

E (focus on the red square you will notice that the concentration - x axis - was very high to reach 50% of the response (EC50) in E unlike A the A concentration was low to reaches 50% of the response (EC50) - remember that the smaller EC50 the higher the potency- so in this curve the potency from high to low: A> B> C>D>E)

- **Which of the following drugs have the lowest efficacy?**

E (focus on the efficacy (response) axis- y axis- you will notice that E has the lowest value unlike C which has a higher value- remember higher response higher efficacy - so in this curve the efficacy from high to low: C>A = B>D>E)

Useful video (:



You must understand these curves as they may come in the exam

QUANTAL DOSE - RESPONSE CURVE

Relates drug concentration to % percentage of patients responding (all or none response), e.g:

- Specified therapeutic response
- Adverse response
- Lethal outcome

- The response may be therapeutic response, adverse effect or lethal effect.

  e.g. prevention of convulsion, arrhythmias or death.

- فكرتة انه يعتمد على فعالية الدواء من عدمها (يا ابيض يا اسود) مثلاً عندي ١٠اشخاص اعطيتهم نفس الدواء ونفس الجرعة اخذ نسبة اللي فادهم واقارنها بنسبة اللي مافادهم لازم تكون نسبة النجاح ٥٠٪ اقل شي (team442)

Used to determine:

01 Median Effective Dose (ED 50):

is a dose of the drug required to produce a therapeutic effect in 50% of individuals.

Dose = concentration

02 Median Toxic Dose (TD 50):

is the dose of a drug required to produce toxic effects in 50 % of individuals.

The clinical trials done on animals only

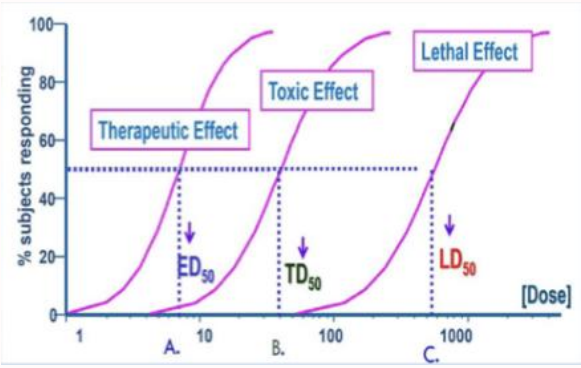
03 Median Lethal Dose (LD 50):

is the dose of a drug required to produce death in 50 % of individuals.

04 Therapeutic index (TI)

Useful video (:

QUANTAL DOSE - RESPONSE CURVE



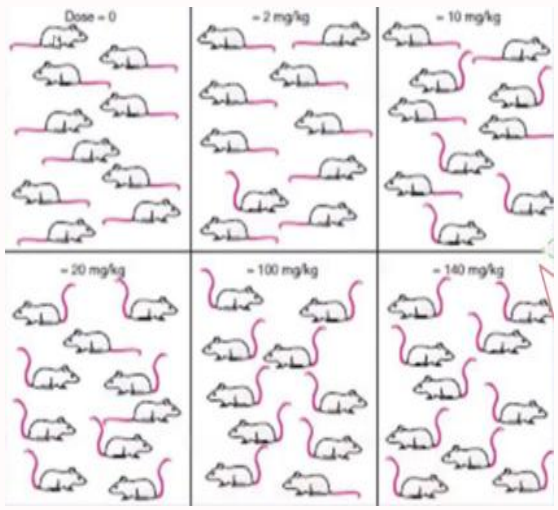
ED 50 = 50% of individuals exhibit the specified therapeutic response

TD 50 = 50% of individuals exhibit toxic effects

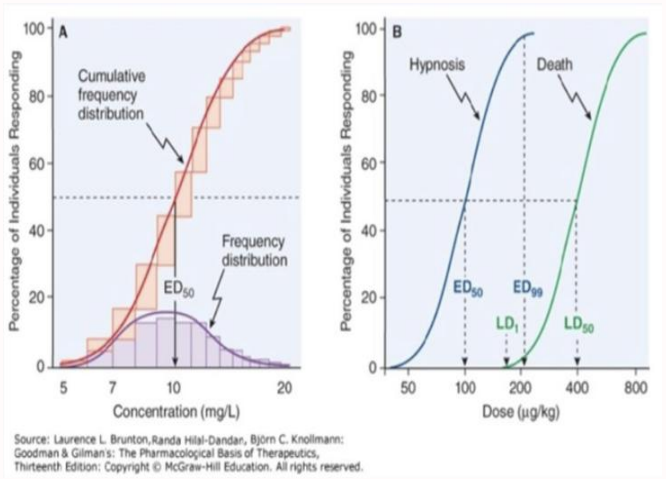
LD 50 = 50% of individuals exhibit death

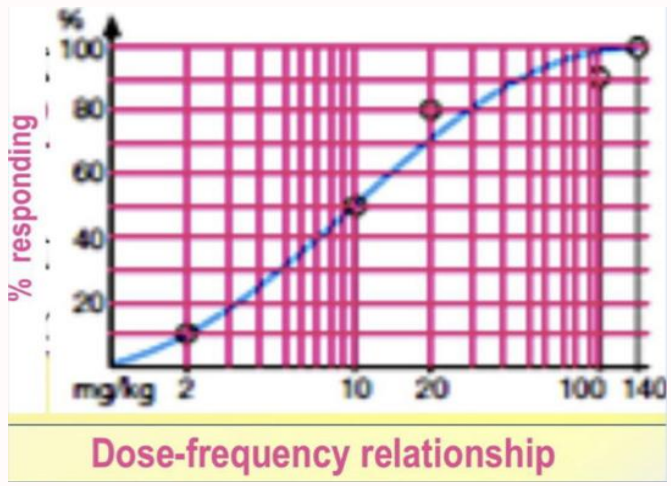
* These predict the safety profile

As dose increase, side effects increase



10 فئران أعطيناهم الدواء لاحظ المرة الأولى مع 2mg فأر واحد فقط استجاب (response), المرة الثانية زدنا hg لجرعة إلى 10mg فاستجاب نصف الفئران، فكلما زادت الجرعة تزيد الاستجابة (response) الى ان نصل الى 100% (team442)





THERAPEUTIC Range (window) VS INDEX (T.I)

Therapeutic range or (window) :

The range between the minimum toxic dose and the minimum therapeutic dose.

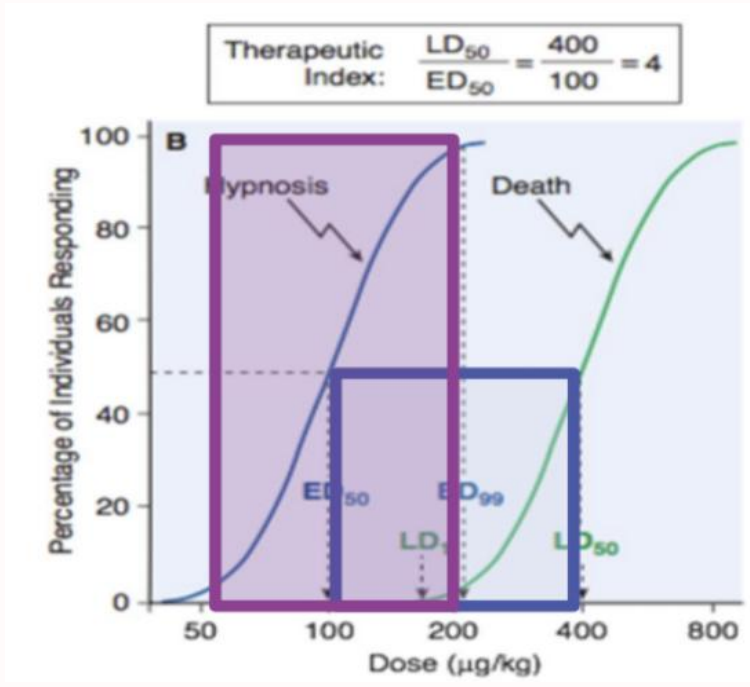
Therapeutic index :

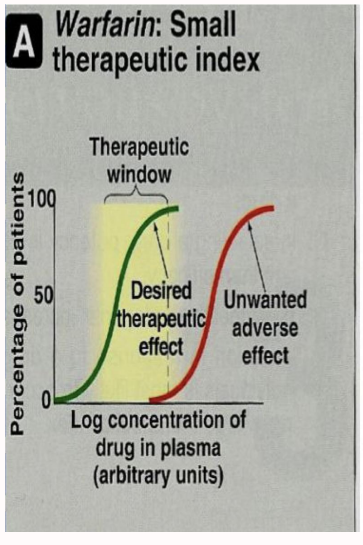
Therapeutic Index = TD50/ED50 OR LD50/ED50

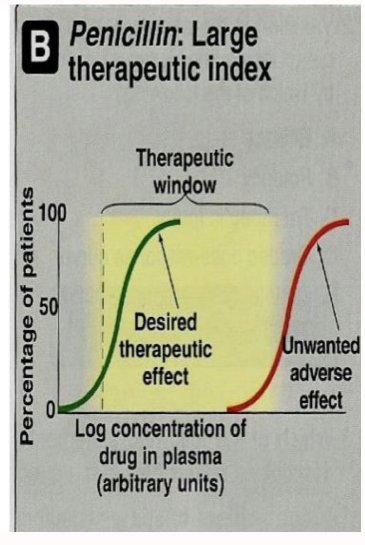
- TD is the dose that produces a toxic effect in 50% of the population.
- LD is the dose that is lethal in 50% of the population 50%.
- ED is the dose that produces therapeutic response in 50% of the population.

It is a measure of the safety profile.

- High value = drug with wide margin of safety e.g. Diazepam,Penicillin (large T.I)
- Small value = a narrow margin of safety e.g. Digoxin, Warfarin (Small T.I) (need therapeutic drug monitoring)







MCQs

1-The ratio of the dose that produce toxicity to the dose that produce a clinically desired effect in a population of individuals is?			
a) Therapeutic index (TI)	b) ED	c) Emax	d) KD50

2-Is a correlation between drug concentration and drug binding capacity at receptors			
a) concentration binding curves	b) graded dose response curves	c) quantal dose response curves	d) None

3-The ability of a drug to combine with receptor:			
a) efficacy	b) Affinity	c) Potency	d) Dose

4-Which of the following drugs has a wide margin of safety?			
a) Chloramphenicol	b) Warfarin	c) Penicillin	d) Digoxin

5-The maximum biological response produced by the drug			
a) EC50	b) ED50	c) Bmax	d) Emax

Answers:

1) A
2) A
3) B
4) C
5) D

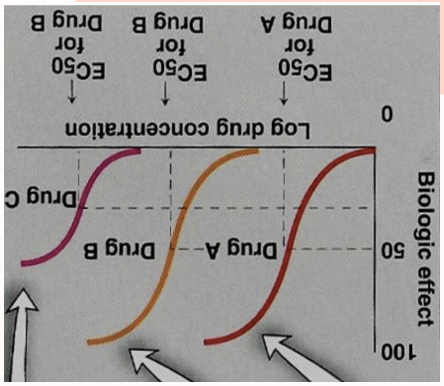
The dose that produces a toxic effect on 50% off the individuals

Define TD50?

A1- Graded dose-response curve

A2- The concentration of drug that produce 50% of the maximum effect

A3-Drug A is more potent than drug B Because A has smaller EC50, Both A And B has the same efficacy because they have the same Emax



Q1- What is the type of the curve? Q2- Define EC50:

Q3-Compare between drug A and drug B on Potency and efficacy

SAQS

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