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MED441
KING SAUD UNIVERSITY

Quantitve Aspects of drug action

Important
Main Text
Male slides
female slides
Extra information
Doctors notes

For any future corrections Editing file

If you didn't understand any part from this lecture Click here

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

QUANTIFY ASPECTS OF DRUG ACTION

Concentration-Binding Curve

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

Dose Response Curves

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

types
- Graded curve
- Quantal curve

AFFINITY → **POTENCY** ← **EFFICACY**

(The **tendency of a drug to bind to the receptors** is governed by its affinity.)

(The **ability for it, once bound, to activate the receptor** is denoted by its efficacy)

Concentration-Binding Curve

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

Used to determine

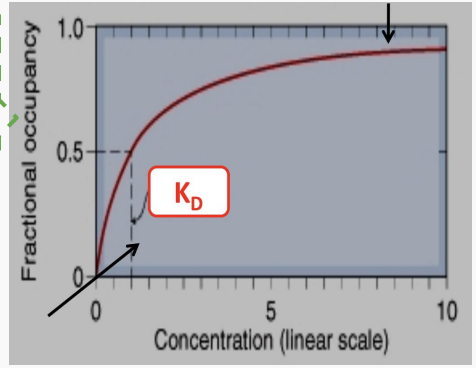
B_{max} (binding capacity) is the total density of receptors in the tissues.

K_{D50} is 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, t**he lower is the KD**
i.e. **inverse relation** (Binding Potential = Bmax /KD)

(Bmax)

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

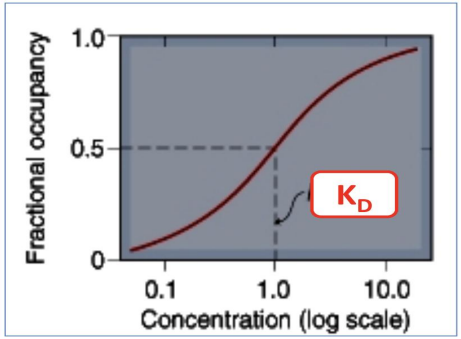


The higher the concentration, the higher the drug binding is going to be. Direct correlation (علاقة طردية) until it reaches Bmax.
يعني الين ما تمتلي ال receptors

كلما قلت K_D كلما صار افضل للمريض ؛لانه ال affinity for drug راح تكون عاليه فيعطي تأثير أفضل.

(Bmax): Total density of receptors in the tissue

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



Dose-response curves

- Is 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.
- i.e. relation between concentration & Response

1- Graded Dose-Response Curve

- Relate drug concentration to response.
- Response is gradual.
- Continuous response: gradual increase in response by increasing the dose. يعني للادوية اللي لازم يستمر عليها
- e.g.blood pressure, heart rate, blood glucose level, cholesterol,...
- Curve is usually sigmoid in shape شكله زي ال (s)

Used to determine

(Emax) Maximum Efficacy

is the maximal biological response produced by a drug.

(EC50) Median Effective concentration

is the concentration of the drug that produces 50% of the maximal response (Emax).

439: concentration that **affects** 50% of (Emax)

Potency

the concentration of the drug required to produce a specified response **(50% of the maximal response = EC50).**

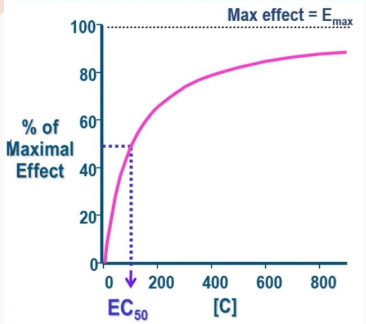
Potency of drugs can be compared using EC50, The smaller the EC50, the more potent the drug.

Potency is **inversely proportional** to EC50

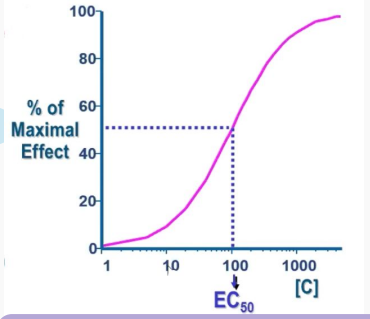
Efficacy

439:The higher efficacy of drug at the Maximum Effect

Graded Dose-Response Curve



As C↑ → response ↑



E_{max}: Effect when all the receptors are occupied by D

EC_{50}: that gives half the maximal effect

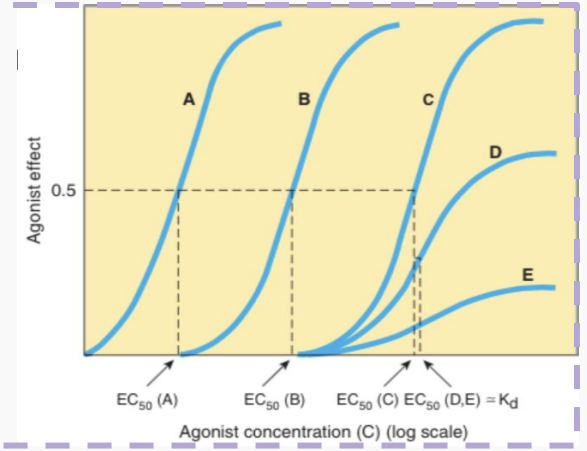
Which of the following curves represent the least potent drugs ?

E

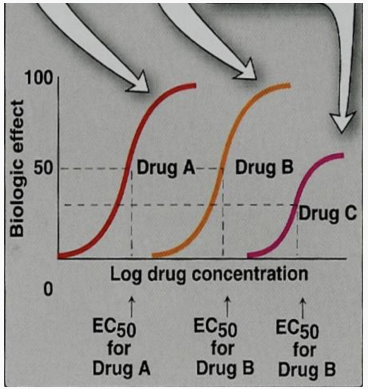
439: concentration يقل potency لانه كلما زاد
Inversely proportional

Which of the following drugs have the lowest efficacy ?

E



Sigmoid shape



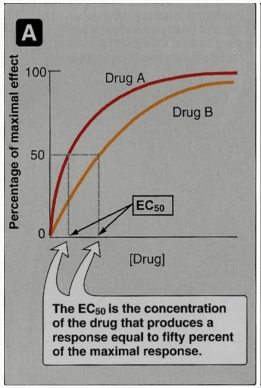
More potent (A>B>C) 435 notes

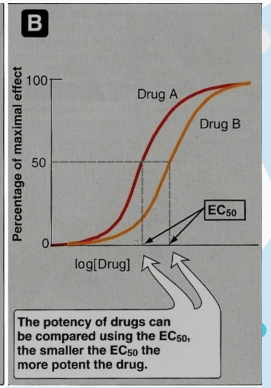
Only in girls slides

Drug A and B have the same **efficacy** but different **potency**, and they have **more** efficacy than drug c.

-Drug A is the most potent

-Drug C is the least potent





2- Quantal Dose-response Curve

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

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

لو أعطيت دواء ل ١٠ اشخاص وابغا اعرف كم الي صارلهم response
لو خمسه منهم أعطوا response يعني 50%. ولو كلهم أعطوا response يعني 100%

Used to determine

(ED50) Median effective dose

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

(TD50) Median toxic dose

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

(LD50) Median lethal dose

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

Therapeutic Index

A measure of drug safety "The ratio of the dose that produces toxicity to the dose that produces a clinically desired or effective response in a population of individuals"

لازم يكون الفرق بينهم كبير علشان ما يوصل لل toxicity

لو حسبت TI وطلع رقم كبير يكون ال drug safe واذا طلع قليل خطير

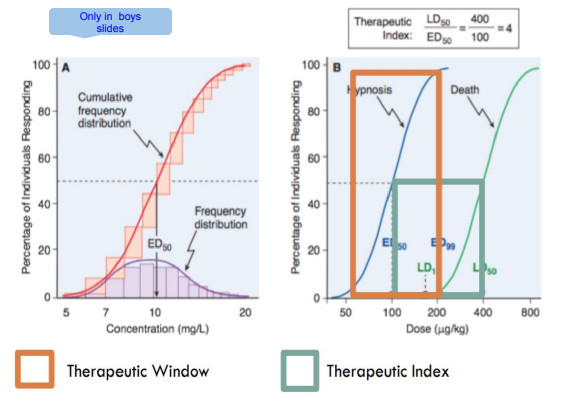
Therapeutic Index = TD50/ED50 or LD50/ED50.

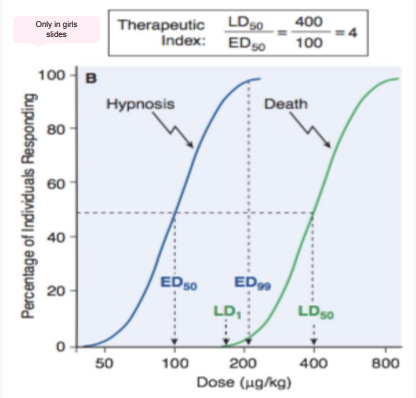
Large /high value = drug has wide margin of safety **e.g. diazepam, penicillin.**

Small value = a narrow margin of safety e.g. **digoxin, warfarin.**

NOTE: The higher the TI the safer the drug

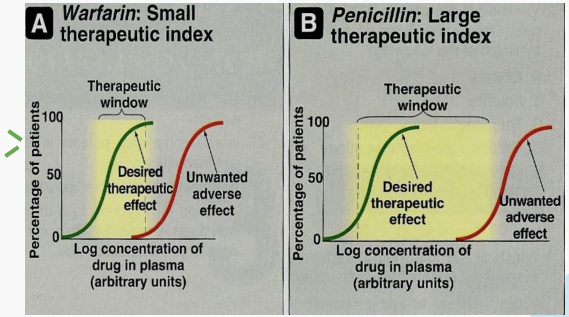
Quantal Dose-Response Curve

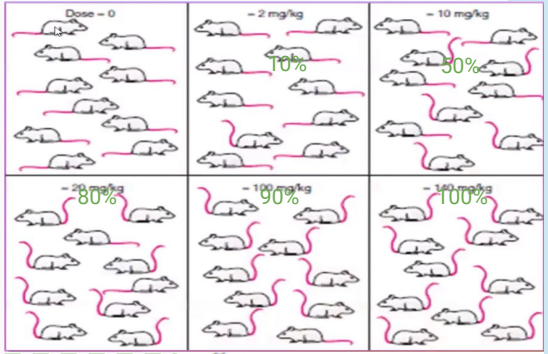


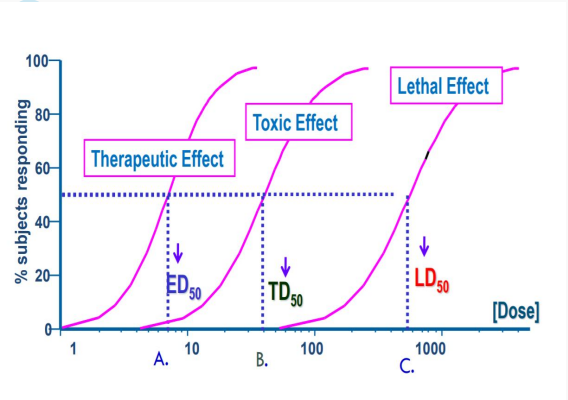


A: warfarin
So close to toxicity

B:penicillin
يطول على ما يوصل لل toxicity
يعني لو المريض اخذ جرعة زائدة ما يؤثر







ED50= 50% of individuals exhibit the specified therapeutic response

TD50= 50% of individuals exhibit toxic effects

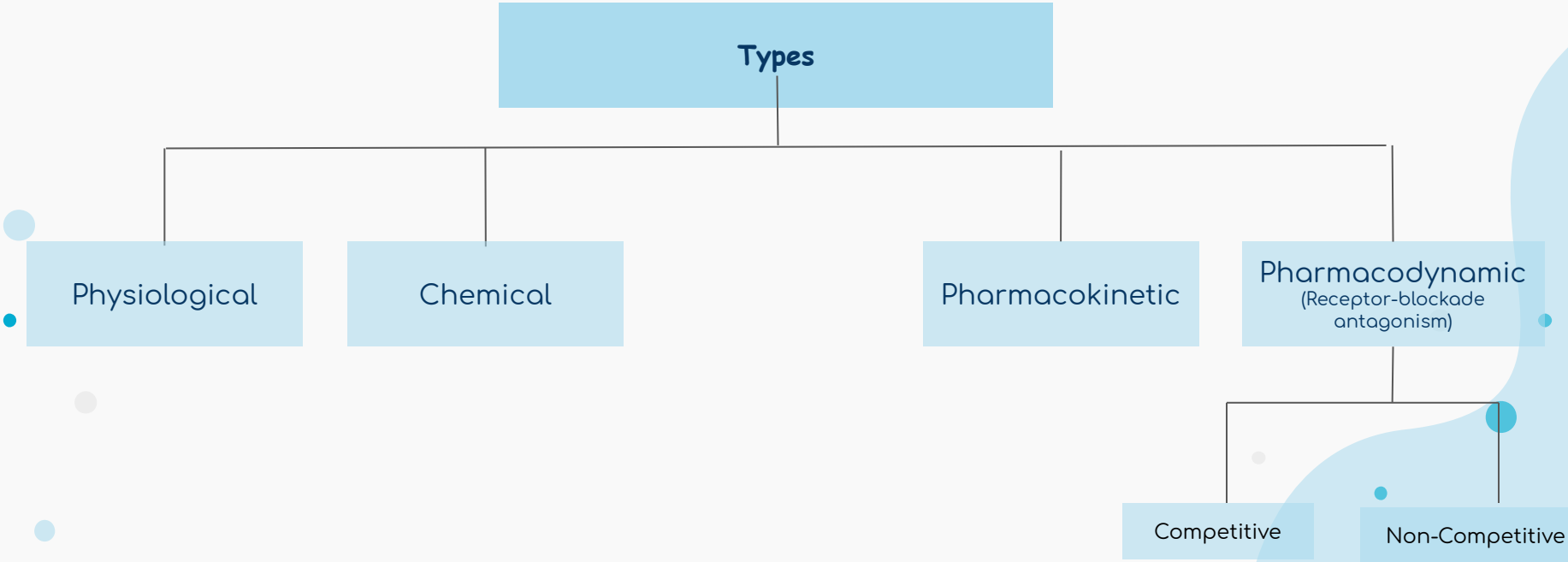
LD50= 50% of individuals exhibit death

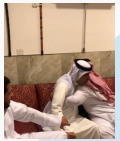
١٠ فئران أعطيناهم من الدواء لكن بس واحد منهم اللي اعطى response يعني 10%

لما زودنا الجرعة صار خمسة منهم اعطوا response يعني 50%

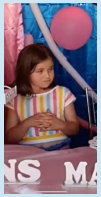
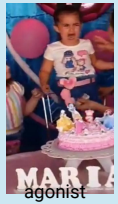
Antagonism

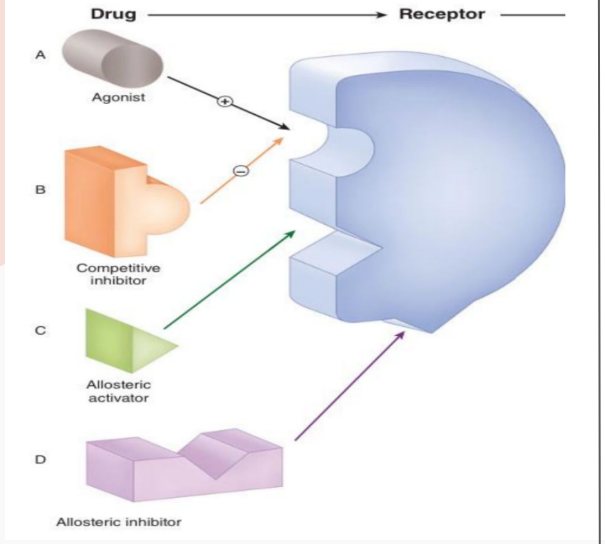
it is the decrease or the complete abolishment of the effect of one drug in the presence of another(
by the co-administration (concurrent administration) مع بعض or combination with another drug).

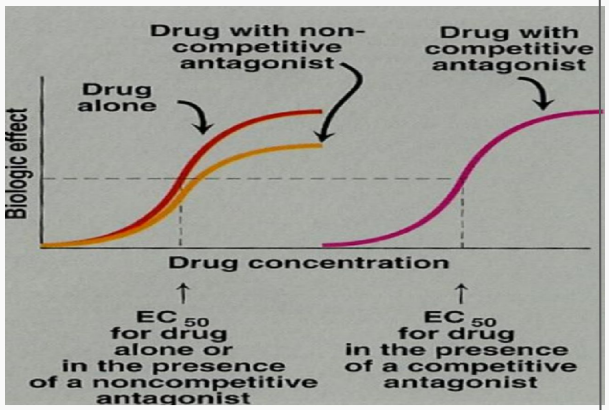


Types	definition	example
Physiological antagonism	Two drugs act on different receptors to produce different **physiological effects** زي لما تكون مشغل المكيف في عز الصيف وفاتح الشباك (شموس vs مكيف بيتكم الضعيّف) *الدكتور ذكر المثال* 	Histamine & Adrenaline **Histamine** → vasodilation → (↓ blood pressure) and bronchoconstriction الهيستامين يخليك مخنوق وما تقدر تتنفس والادرينالين يعطي عكس المفعول **Adrenaline** → Vasoconstriction → (↑ blood pressure) and bronchodilation -Adrenaline is used in anaphylactic shock. 
Chemical antagonism	-Simple chemical reaction between 2 drugs resulting into loss of activity -No receptor.	(**Dimercaprol**) used as antidote reduces heavy metal toxicity (as in **lead toxicity**). للعمال اللي يشتغلون بمصانع الرصاص ، الدواء يمسك ال lead وما يمتصه الجسم ويطلع منه بدون أي ضرر ومثل antacid toxicity
Pharmacokinetic	The antagonist effectively reduces the concentration of the active drug at the site of action.	e.g. (**Phenobarbitone**) accelerates hepatic metabolism of warfarin الدواء خذناه في enzyme induction بالليكتشر الثالث ، تذكر!

Pharmacodynamic

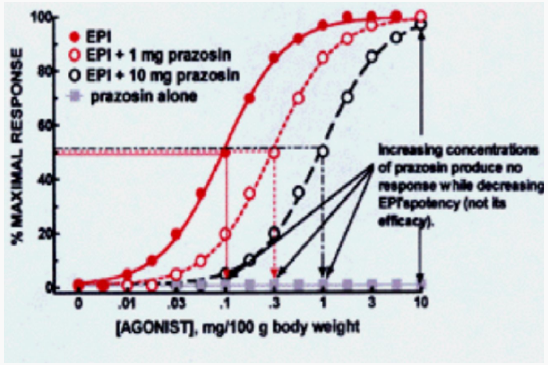
Types		Definition	Example
Competitive	Reversible	-Two drugs compete for the same receptor**(only one bound).** -The antagonist partially or completely prevents the pharmacological effect of agonist. -Antagonist **dissociate** rapidly from receptor. - Antagonism can be overcome by increasing the Concentration of the agonist. - Parallel shift of the curve to the right, without any change in slope or maximum نفس المستوى بس تركيز أعلى زي الصورة بالسلايد الجاية هذا النوع (البقاء في الباوند للأكثر تركيزًا)	Acetylcholine atropine
 وضعهم مع الرسبتور	Irreversible	-Two drugs compete for the same receptor. **-Antagonist** forms stable, permanent chemical bond with receptor. -The original response **can not be overcome** even by increasing the dose of the agonist. -No parallel shift of D-R curve -A decrease in slope and a reduced maximum are obtained.	phenoxybenzamine noradrenaline.
Non-Competitive  antagonist ما يتنافس بس وضعه تخريب  agonist	-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		verapamil noradrenaline

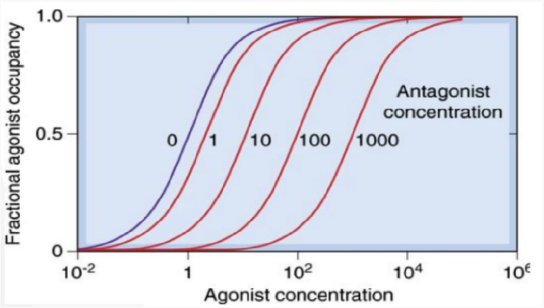




صور توضيحية للسلايد الماضية

Competitive reversible antagonist

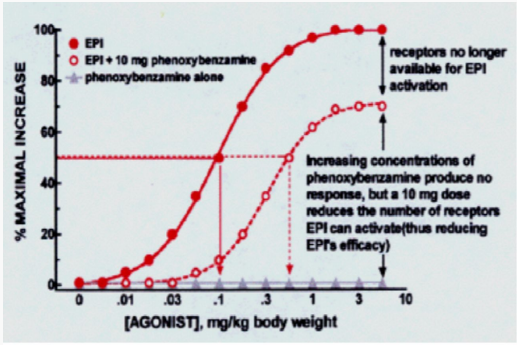


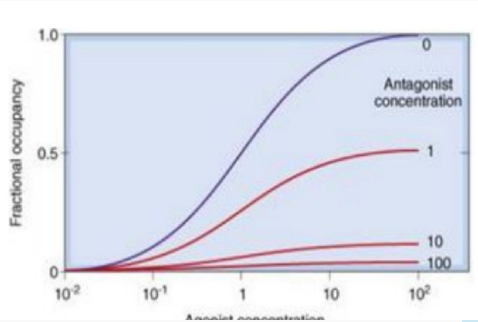


-Parallel shift to the right.
- No change in slope or maximum.
-Agonist is able to reverse the antagonist.

vs

Competitive irreversible antagonist





-No parallel shift.
-Decrease in slope and a reduced maximum.
-Agonist has no effect on the antagonist

Thanks to 439

In girls slides

Antagonism can be overcome by increasing concentration of agonist = SURMOUNTABLE

Antagonism cannot be overcome by increasing concentration of agonist = NON-SURMOUNTABLE

EC100

-When a drug binds to a receptor with mass action rules, the fraction occupancy equals D/(D+K)

-It is impossible for a drug concentration to reach EC100 and EC0.

-Even if you increase D to a million there will always be a K in
the denominator and as such will never truly reach EC100.

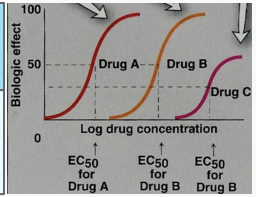
439

D= concentration of drug

K= equilibrium binding dissociation constant

MCQ:

1-Which of the following curves represents the most potent drugs?			
A) curve C	B) curve A	C) curve A&B	D) curve B



2-A 5 years old boy accidentally took iron overdose, which of the following would reduce the drug toxicity?			
A) Dimercaprol	B) Phenobarbitone	C) Adrenaline	D) Histamine

3-Which type of antagonism requires no receptors? (439)			
A) Non-competitive	B) Competitive	C) Chemical	D) Physiological

4-the relationship between the affinity of Drug for receptor and the KD is?			
A) linear relationship	B)Inverse relationship	C) Direct relationship	D) No relationship

Answers

1	B
2	A
3	C
4	B

MCQ:

5-Is the concentration of the drug required to occupy 50% of receptors at equilibrium?			
A) KD50	B) EC50	C) TD50	D) LD50

6-Antagonism that can get be overcome by increasing the concentration of the agonist?			
A)irreversible	B) Non-Competitive	C) reversible	D) Physiological

7- Antagonist effectively reduces the concentration of the active drug at the site of action?			
A) Pharmacodynamic antagonist	B) Chemical Antagonism	C)Physiological antagonist	D)Pharmacokinetic Antagonism

8-Which of the following used in anaphylactic shock?			
A)Dimercaprol	B) Adrenaline	C) Histamine	D) Colchicine

Answers

5	A
6	C
7	D
8	B

SAQ:

A) Two drugs act on different receptors to produce opposite physiological effects?

B)Quantal dose response curve is used to determine?

C) A drug with TD50=1000 and ED=2 measure the Therapeutic Index?

D) Compare between competitive reversible and competitive Irreversible antagonism

A) Physiological Antagonism

B) ED50, TD50, LD50, Therapeutic index (TI).

C) TI= 1000/2 =500

d) on slide 11

Thank you

Team leaders

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