Lecture 10

Pharmacology

رامي القضاة

آيه عبيدات

Second Year

Passion Batch

Drug Antagonism

pharmacodynamic Antagonism by receptor block

Antagonists in this sense are drugs that bind to receptors but do not activate them and thereby it decrease the effect of an agonist

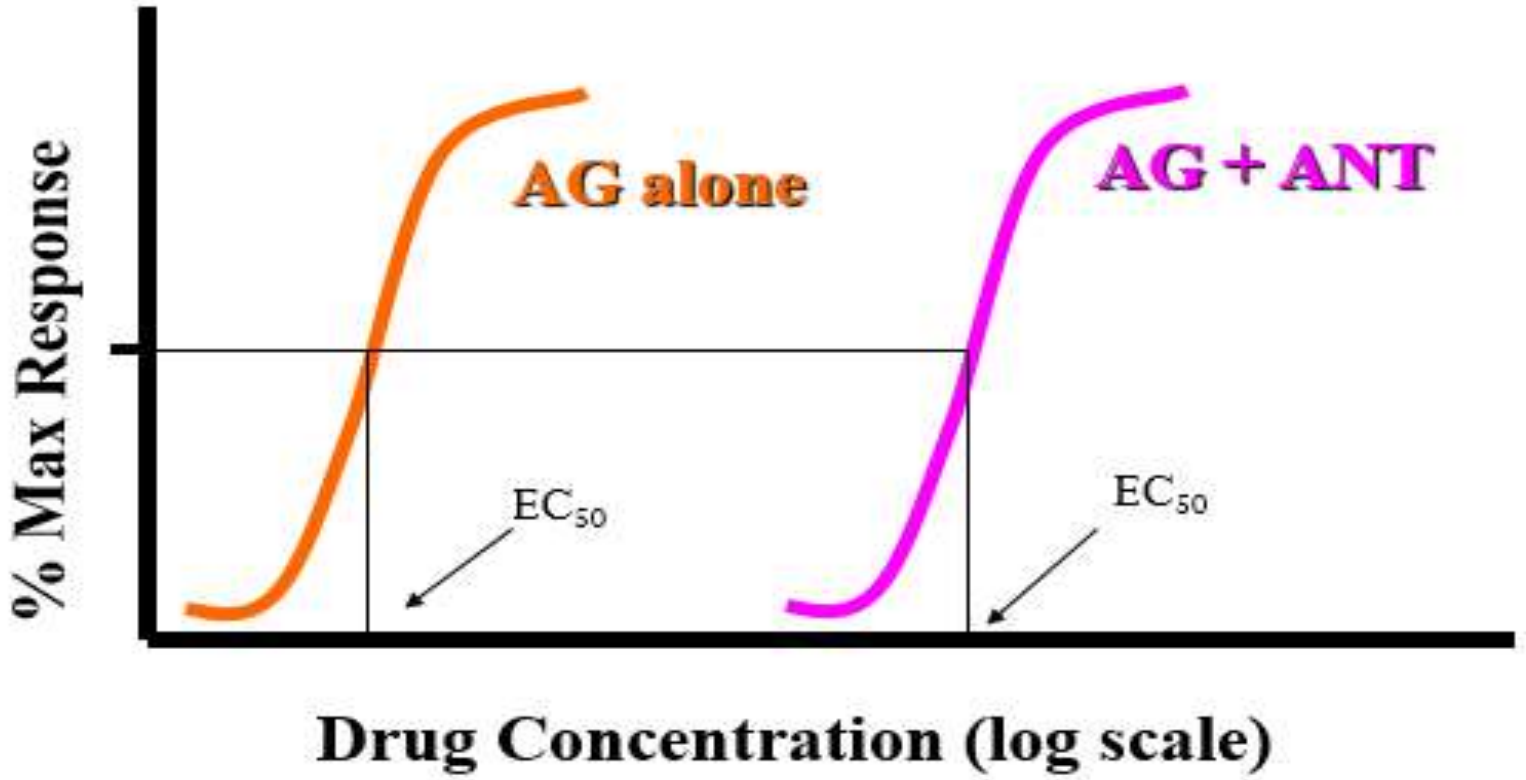
A) competitive (reversible) antagonism:

- **Competitive antagonists bind reversibly with receptors at the same site as the agonist but induce no action – they block the receptor for agonist**
- **The response can be returned to normal by increasing the dose of agonist.**
- **The ability of higher doses of agonist to overcome the effects of the antagonist ⇒ a parallel shift of the dose-response curve to the right**

Drug Antagonism

- ***A) competitive (reversible) antagonism:***
- **The maximum response is not depressed**
- **e.g., *Propranolol competes with the endogenous ligand, norepinephrine,* at β-receptor**

Competitive Antagonism Shifts The Agonist D-R Curve (*Potency*)



1

- Drug antagonism = Drug interaction
- There are 2 types of drug antagonism at receptor sites :
- competitive (reversible) & non competitive (irreversible)

1) Competitive :

- both can bind with different affinity, but when one drug increase in concentration the other dissociate

هاي الحاله بتصير لما نعطي دوايين ويكونو Agonist + antagonist دايما ال antagonist

بكون عنده High affinity to the receptor (بحب يرتبط اكثر)

2

معظم ال Drug الي بكون () بجسمنا احنا بنعطيه للجسم يعني خارجيه لكن فيه مواد بتعالج جسمنا تصنع داخلياً يعني بتكون Endogenous compound .

مثال : لما اعطي β-blocker ال β-blocker لحتى يرتبط مع β-receptor وبكون عنا Normal noradrenaline لهيك لما نعطي هاذ ال Antagonism رح يرتبط بالاول ويعمل block لل receptor ← Then do the action

بعد هيك رح يضل موجود ؟؟؟ لا

الي بصير انه ال Adrenaline الي بجسمي بتجمع حول ال receptor ← **By higher concentration it will dissociate**

3

عشان هيك بنفسر معناه انه :

-competitive : because they compete to the same receptor.

-reversible: because by increasing the agonist dose it will be reversed.

- ومعظم الادويه بتكون Reversible لانه لو كانت irreversible متى راح يطلع الدواء؟ و اما راح يصير : More action or side effect

- مثال: Propranolol (β-blocker)

- propranolol will blocked β-receptor ...then… after doing the action noradrenaline will increase by time and will dissociate it then it will go to normal.

4

- ال Agonist هو noradrenaline (بالنسبه لجسمنا) وكانت تشتغل عادي ليش بطلت ؟
لانه عندي Block receptor لهيك لازم يرتفع تركيز ال noradrenaline اكثر لحتى تطلع ال Antagonist يعني : ال adrenaline اقل potency .

- نفس الاشي لو اخذت 2 drugs from out side the body و كانوا **Agonist + antagonist**
راح يصيرلهم Drug –drug interaction وبالتالي الي رح يرتبط ال antagonist فبالنسبه لل Efficacy ما بتتاثر لانه لما يعمل block رح يعطي كل ال **zero action or negative action**
لكن لما يرتبط لل Adrenaline حيعمل full action فهو مسألة Dose + concentration

Drug Antagonism

- ***B) Non-competitive antagonism:***
- **There is a decrease in the maximum response present without a DRC shift by :**

➢ **Antagonist binds with the same site as the agonist but dissociates very slowly, or not at all, from the receptors (due to the covalent bond)**

- **⇒ no change (or nearly no change) in the antagonist occupancy when the agonist is applied.**
- **Irreversible competitive antagonism occurs with drugs that**
- **form covalent bonds with receptors**

- **either prevents binding of the agonist or prevents the agonist from activating the receptor**

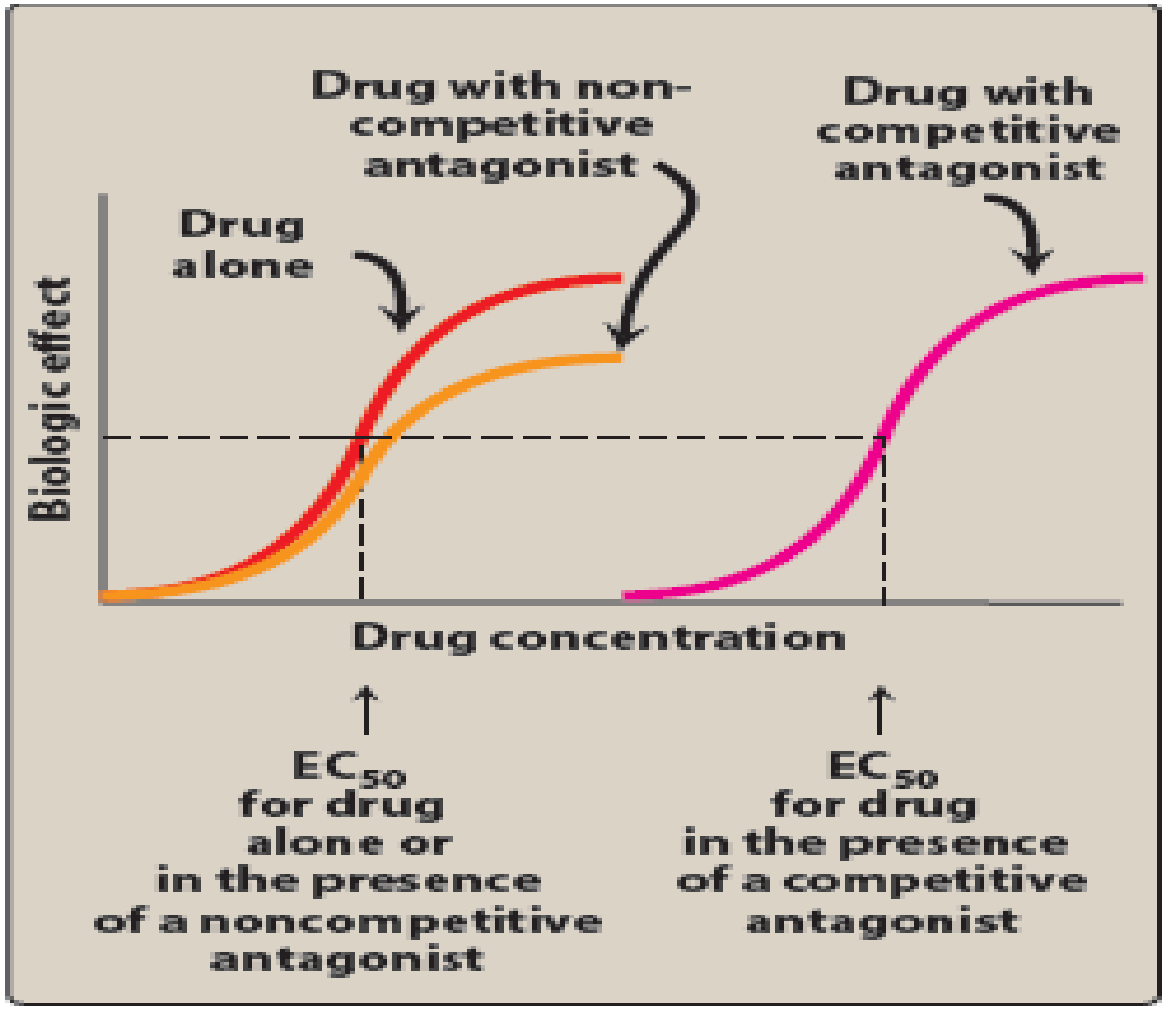
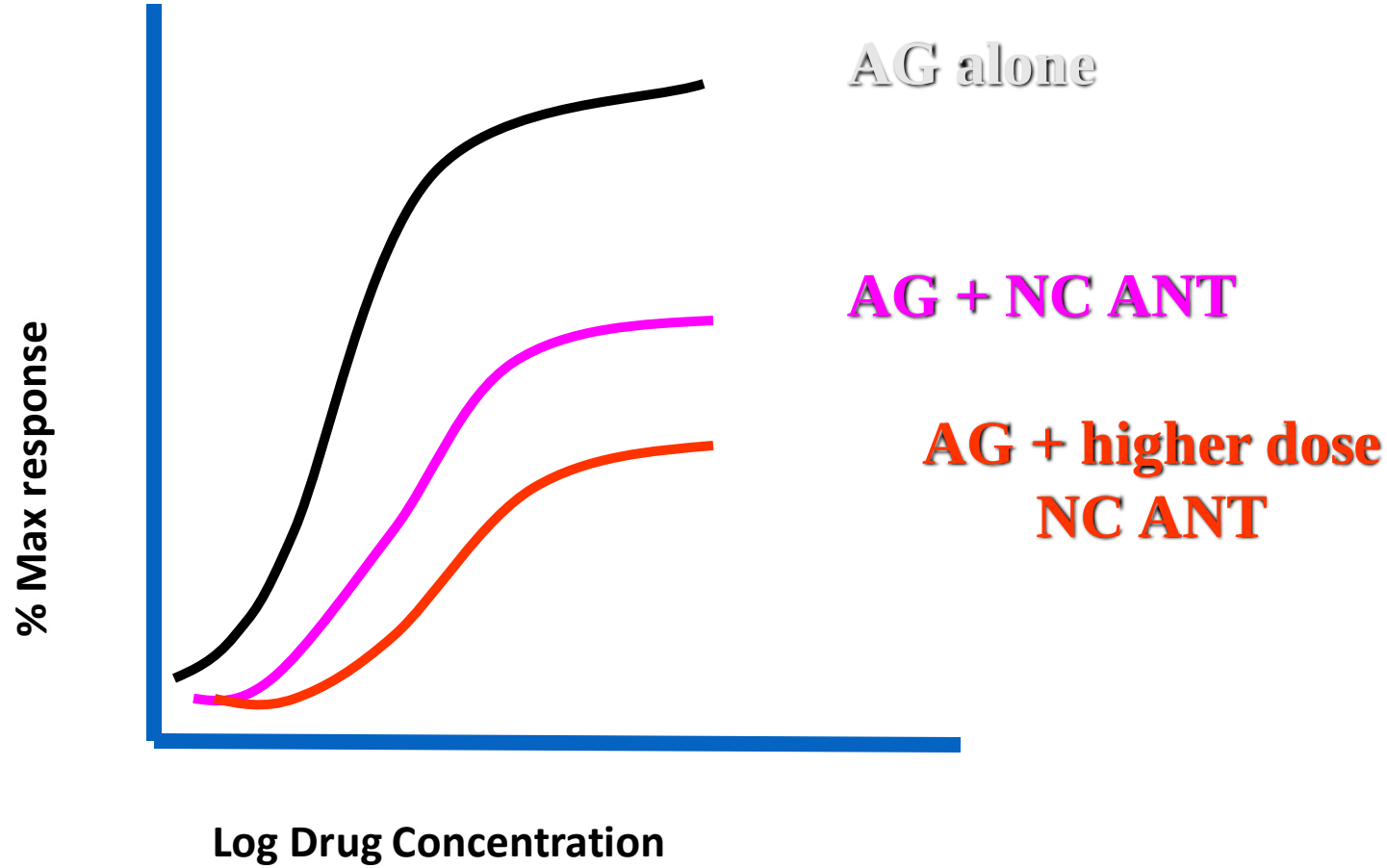


Figure 2.12
Effects of drug antagonists. EC_{50} = drug dose that shows 50 percent of maximal response.

Noncompetitive Antagonism Decreases Agonist *Efficacy*



2) Non-competitive : drug will bind at the same receptor sometimes or at allosteric.

– يعني ال Receptor مش موقع واحد .. يعني ممكن يجي يرتبط من الجنب فهو فعلياً Not occupied(غير مشغول) لكن بيعمل conformational change فما بخليه الثاني يعني هو ممكن يعمل على Another sideمش حقيقي اسمه allosteric side

- so, non-competitive mean : drugs don't compete at the same side

وهذا يعني انه لو زدنا ال Dose لواحد ما راح يطلع الثاني

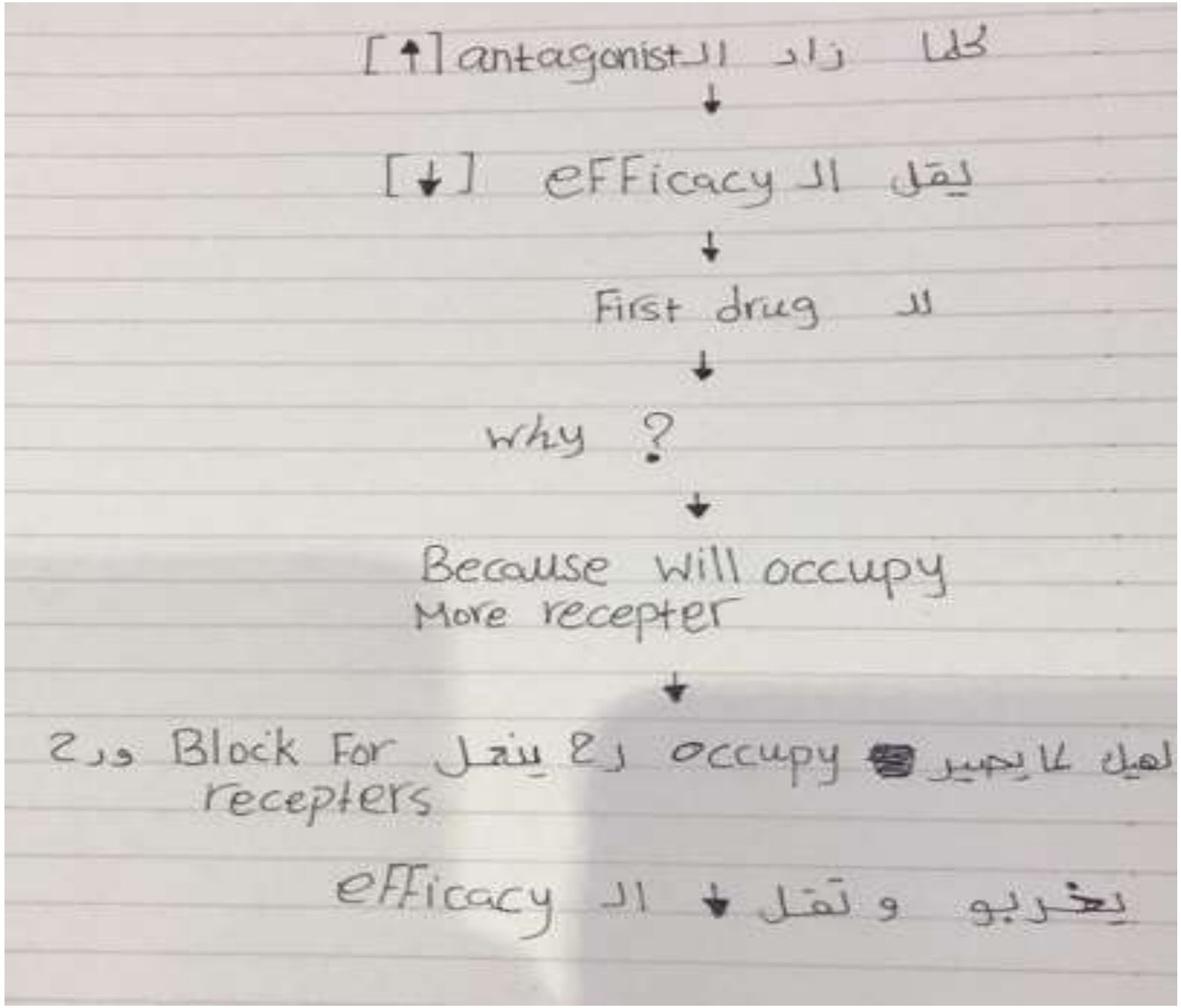
وهاذ الاشي بصير ببعض ال Enzyme وممكن تعمللنا تسمم وافضل مثال للتسمم هو ال Insecticides بعمل ماده بتشبه (cholinergic receptor blocker) لما ترتبط مع Phosphoacytlcholine enzymeرح يرتبط مع ال irreversible .....

6 ... هي اكثرها تسمم + غير مرغوبه + الادويه ما فيه كثير منهم Irreversible ليش؟

لانه لو ارتبط Drugووجهتله antagonistوالي هيه noncompetitive +irreversible رح تعمل Covalent bondمع ال receptorفما بتتفكك

كأنه هو سكرلي ال Blockفبالتالي لو تزيد الجرعه ما رح يعمل dissociateفراح يعمل occupationلبعض ال receptorويخليله شوي فبالتالي أثر على الفعاليه (efficacy) يعني حيقلل مفعول ال Agonistلكن لو زدت الجرعه (increase dose)اغلب الdrug مش راح يصيرله dissociate.

7


[↑] antagonist الـ زاد كلما
[↓] efficacy الـ يقل
First drug الـ
why ?
Because will occupy
More recepter
Block For يشغل ر٤ occupy لهيك مايصير ور٤
recepters
efficacy الـ ↓ و تقل يخربو

• Other Drug Antagonism

• **Antagonism: The effect of one drug is diminished or abolished in the presence of another drug.**

• **Antagonists: drugs that decrease or oppose the actions of another drug or endogenous ligand.**

• **An antagonist has no effect if an agonist is not present.**

1. **Pharmacodynamic (receptor) antagonism**
2. **Physical antagonism**
3. **Chemical antagonism**
4. **Physiological antagonism**
5. **Pharmacokinetics antagonism**

• Drug Antagonism

1. **Physical antagonism**

➢ **Example: Charcoal adsorb drugs like alkaloids**

2. **Chemical antagonism**

• **Interaction of two substance based on their chemical properties ⇒ a loss of all effects of a drug (e.g., chelators bind the metal ions to form an**

• **inactive complex,**

• **Examples:**

➢ **protamine sulfate (weak base)- ionically binds to heparin)(weak acid).**

➢ **Heparin + Tetracyclin**

➢ **Tetracycline and iron, AL+3**

- **3. Physiological antagonism**
- **⇒ when two drugs act on separate physiological systems and**
- **produce opposite actions.**

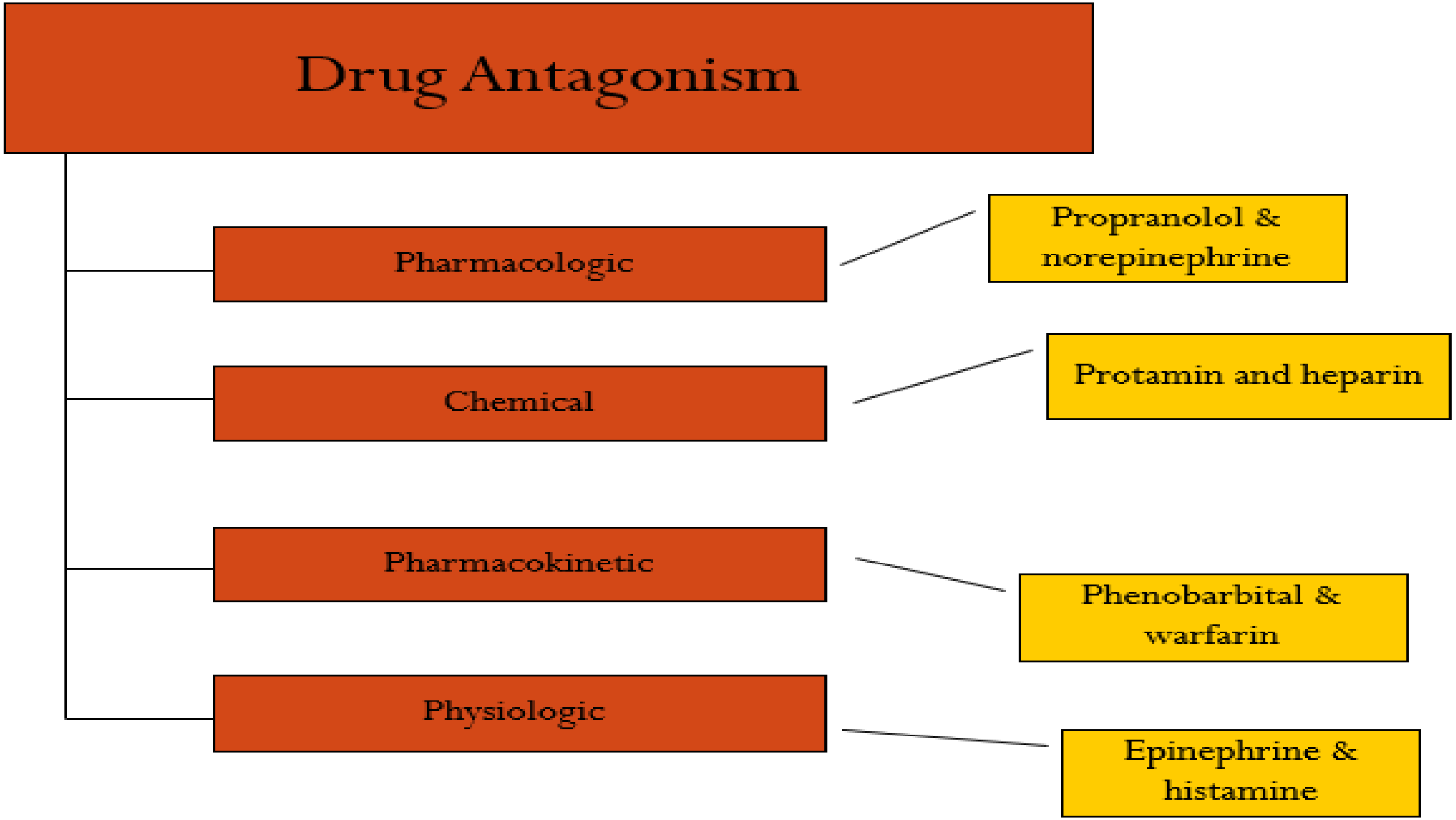
- **Many drugs may interact with various types of the receptors producing opposite effect**

- **Examples**
- **- Bronchoconstriction after histamine - mediated by H_1 receptors - vs. bronchodilation after Epinephrine mediated by β_2 receptors.**

- **Glucagon and insulin**

• Drug Antagonism

- **4. Pharmacokinetic antagonism**
- **"Antagonist" reduces the concentration of active drug at its site of action**
- **in various ways:**
- **e.g., an increase of the biotransformation (metabolism) of the**
- **Anticoagulants (e.g, warfarin) during the use of phenobarbitone (enzyme induction),**
- **Or increase in the excretion**
- **Or decrease in absorption : antacid and ketoconazole**


Drug Antagonism
Pharmacologic
Propranolol & norepinephrine
Chemical
Protamin and heparin
Pharmacokinetic
Phenobarbital & warfarin
Physiologic
Epinephrine & histamine

- Types of drug-drug interaction:

1- chemical : it's basic & acidic….. We need it sometimes

For example: if we want to neutralize Acidity of the stomach we need

--sodium bicarbonate or – aluminum hydroxide which is basic so, I can solve my problem when I used chemical interaction.

- Ketoconazole need acidic media and it's antifungal …. So, if you give antacids with ketoconazole it will not be dissociated + no absorption + no treatment……. Treatment failure = 90% so, it decrease the efficiency.
- As we mention previously, ketoconazole is antifungal we use it to treat Fungal diseases that may cause mycosis in the liver & nail.
- ……

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- …. So, This drug must taken when the acidity of the stomach is high and we can't take any type of antacid when we take it.
- The best time to take ketoconazole after food….because PH decreased to 2.5 .
- Sometimes chemical antagonism is good for our bodies like in heparin

- Heparin : = anticoagulant & given subcutaneous & have narrow therapeutic index & increasing the dose causes bleeding
- Heparin is antidote
- Antidote means : drug giving in emergency uses to reduce the efficiency of a drug that cause toxicity.
- Heparin is weak acid when it reach the plasma and we have toxicity … we give protamine sulfate which is basic antidote and it is in plasma not in stomach so I'm already give sc then we give IV protamine sulfate that will decrease the action then stop the action of heparin by binding it that make (null-no active) salt

- Many things may cause halation which mean: complexion between drug and iron like heme in the blood.
- tetracycline which is a drug for acne can't be taken by (iron, calcium or milk) …… if they taken together the drug will not be absorbed & it will be eliminated with GIT without any effect.

-Take the first drug and after 3-4 hours at minimum take the other drug

- why 3-4 hours ? Because it is the gastrin emptying time.

2-Physical: as chemical when we reach toxic dose we can avoid it by:

- Gastric lavage & - charcoal

- خلال اول ساعتين من اخذ الجرعه

3- Physiological: Drug وبدنا نقيس عليها الPhysiological action بصير بجسمنا كثير

1- مثل ما ناكل بينفرز insulinوشوي glucagonوممكن كل واحد فيهم اله receptor لكن شغلهم متضاد

2- β1 agonist in the lungs causes bronchodilation and we have epinephrine in our bodies ….. If we need drugs like salbutamol and Ventolin which causes bronchodilation too.

- Histamine:

H1 receptor in the brain which causes allergic reaction

H2 receptor in the stomach

Histamine will cause bronchoconstriction (allergic reaction) ….. We can treat it by adrenaline in emergency cases……

12 ….. So, histamine and epinephrine have different receptors :

Histamine: H1 receptor

Epinephrine: β1

= the final action : bronchodilation

وبنقيس على هذا المبدأ كثير ادوية مثل ادوية الضغط -

We also have drug- disease interaction & food- disease interaction

For example : voltaren يوخذ ممنوع مريض الازمه

- drug-drug interaction is very significant for narrow therapeutic index like warfarin.

- When we have a problem in the metabolism of the drug we have : inducer & inhibitor

لو اعطينا 2 drugs وعملوا inducer هون لازم نتدخل وبركز على مين تأثر واذا كان Narrow or not واحتمالية انه يكون الدواء narrow therapeutic index مش كبيره

- لهيك لما يصير drug inducer :

اما ببطل Drug A وبخلي B

اشيل B واخلي A

ازيد جرعه واقلل جرعه

- غير هيك ما فيه Splitting the time لانه بيعتمد على ال half time وكلهم حيلتقوا في ال Metabolism phase.... يعني الانزيم لحتى يصيرله inhibition or inducer بده يومين

So, drug interaction will not occur at the time we take the drug because any enzyme has a half time for inhibition so, we can't guess.

يعني الان انا بشوف مين الي متاثر, مثال : لو اعطيت Warfarin طلع من المستشفى وتمكن بعد اسبوعين من كتابة الوصفه و بحكيلك انه عندهBleeding مثل دم متجلط او Blood in urineفبنرجع نعمل checkلل prescription... هو عنده inhibitor لانه ال Warfarinلما يزيد تركيزه بيعمل bleeding

فبالتالي اذا الدواء الثاني الي بنوخذه كان مهم ولازم اخليه بعمل تقليل للDose وبنعمل Monitoring

- طيب لو اكتشفت انه الدواء الثاني مثل ال Cimetidine drug (دواء للحموضه) بخلي الwarfarinوبشيل ال cimetidineوبحطله famotidine لانه ال famotidine ما بيعملDrug inhibition اذاً الان بقدر اتحكم بالثاني ولكن ما بقدر اقله خذ واحد الصبح وواحد المساء

Therapeutic index

- The therapeutic index of a drug is the ratio of the dose that produces toxicity to the dose that produces a clinically desired or effective response in a population of individuals:

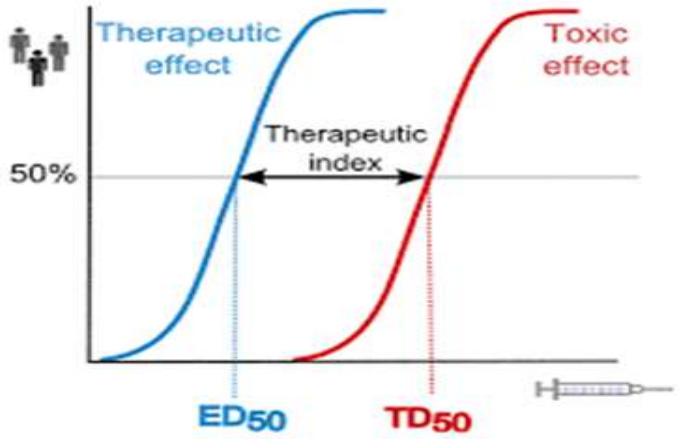
$$TI = \frac{TD50}{ED50}$$

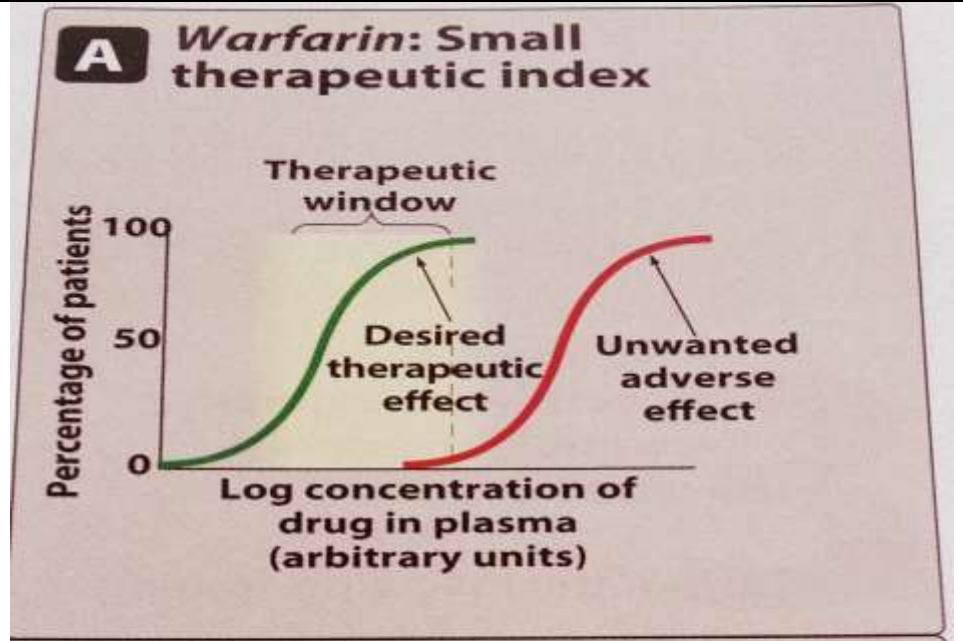
- Where: TD_{50} = the drug dose that produces a toxic effect in half the population
- ED_{50} = the drug dose that produces a therapeutic or desired response in half the population.

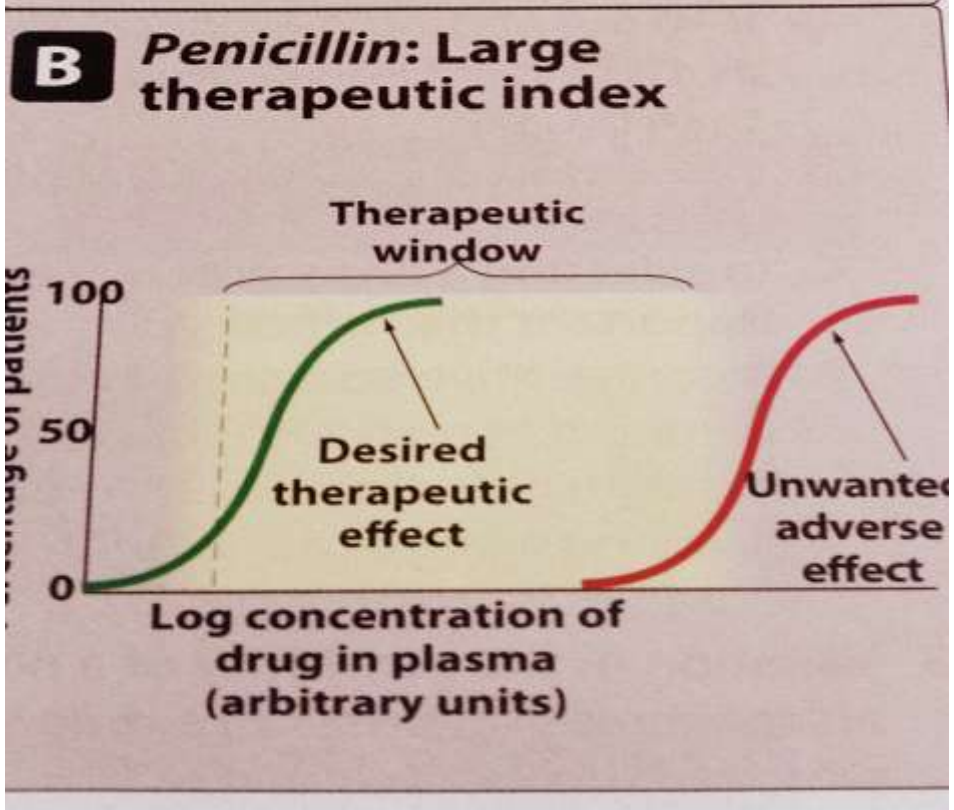
Therapeutic index

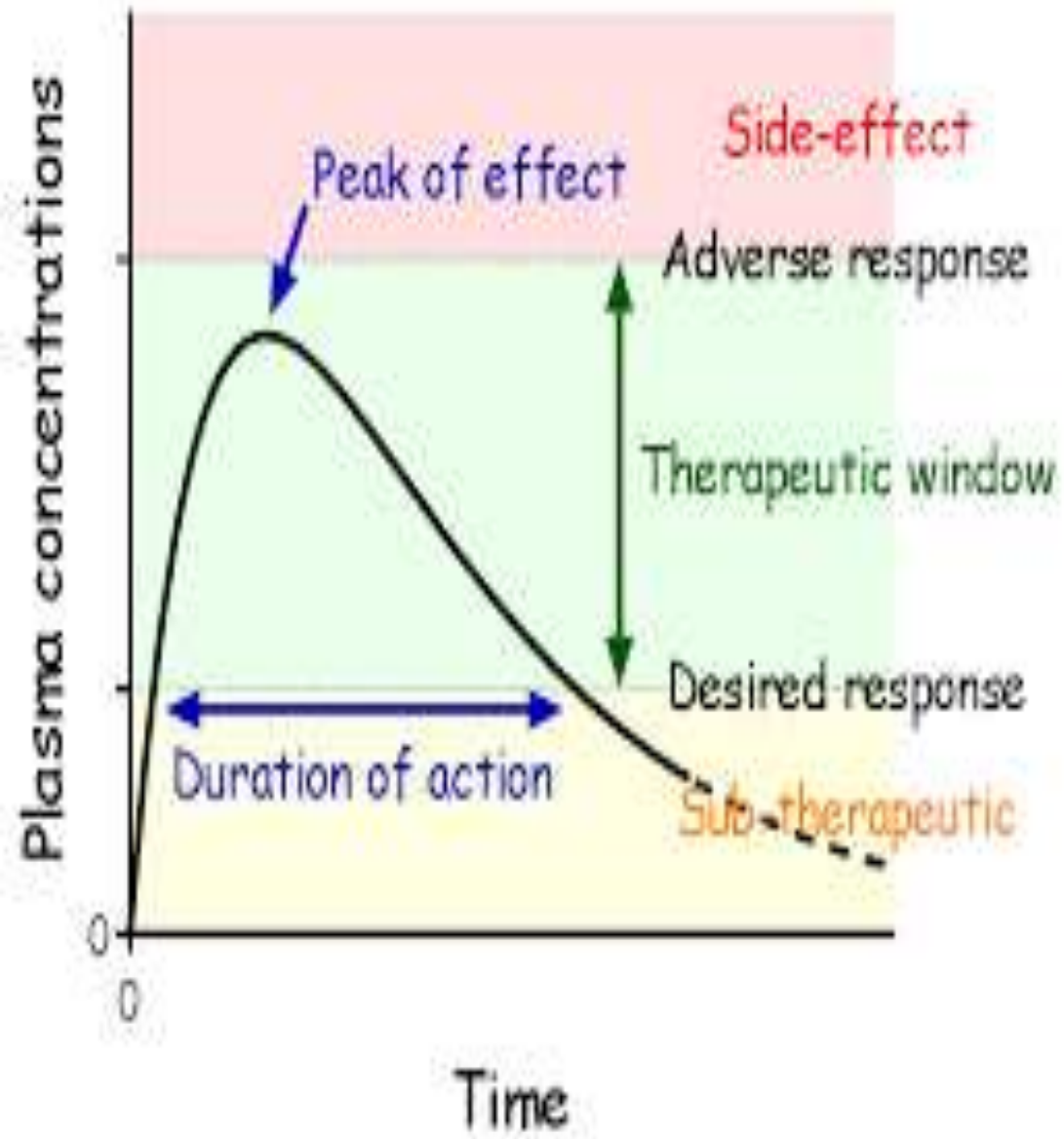
- therapeutic index is a measure of a drug's safety,
- a larger value indicates a wide margin between doses that are effective and doses that are toxic.

- Warfarin (example of a drug with a small therapeutic index)
- Penicillin (example of a drug with a large therapeutic index):




A
Warfarin: Small therapeutic index
Therapeutic window
Percentage of patients
100
50
0
Desired therapeutic effect
Unwanted adverse effect
Log concentration of drug in plasma (arbitrary units)


B
Penicillin: Large therapeutic index
Therapeutic window
100
50
0
Desired therapeutic effect
adverse effect
Log concentration of drug in plasma (arbitrary units)


Plasma concentrations
Side-effect
Peak of effect
Adverse response
Therapeutic window
Desired response
Duration of action
Sub-therapeutic
0
0
Time

- Therapeutic index : indicators for safety and toxicity …. It's number Calculated by knowing the lethal dose.

- كم الجرعه الي حتسبب تسمم او قتل ؟ 50 % من ال Population

يعني مثلاً: بكون عنا عدد من الRat(تجربه بتصير على ال rat وال Human)

بضلهم يزيدوا العدد ليقتل 50%..... من العدد الي هيه Lethal

لو كان عندي ال Lethal =250 وال Dose=50 ..... 250 /50=5... وكل ما قل معناها ال Therapeutic index قليله.

- Therapeutic window : it's the algebraic difference between toxic dose and therapeutic dose (toxic dose – therapeutic dose)
- Example : therapeutic dose= 1 …… toxic dose = 15

  therapeutic window = 14

- Therapeutic index and therapeutic window are indicators for safety but we can't compare between them ……. We must compare between index & index or window & window.

البندول ..... الحبه = 500 مليجرام .. مسموح باليوم 4 جرام .. متى ببلغ ال Hepatic toxicity

عند 10 جرام يعني 20 حبه طيب الLethal dose ؟ عند 15 جرام وفي حالة الصيام عند 12 جرام .

لنفترض لو كان 15 جرام والحبه 500 مليجرام كم الجرعه ؟

30=1500/500

- Drugs with narrow therapeutic index: digoxin, warfarin, lithium, phenytoin.
- Drug with large therapeutic index : penicillin, paracetamol.

Penicillin-

لازم ازيد الجرعه كثير لحد ما يعطيني بداية ال toxic هسا هون ما بنحسب بداية ال lethal هون بداية ال side effect اللي هيه ال **unwanted adverse effect**

- Large therapeutic index = SAFE

دوري في ال Absorption = splitting the time

دوري في الmetabolism = لازم اغير واحد فيهم او ازيد او اقل جرعه

متى بتوقع الDrug interaction؟ - لما يكون المريض بوخذ ادوية كثير (Polypharmacy)

- كمان لما يكون كبير بالسن(multi diseases)

- Problem in liver or kidney.

- لازم دايماً ندرس ال Pharmacokinetic of different population

لانه ال Pediatric بيختلف عن

17

بدنا نحكي عن ال GrapFruit it's
enzyme inhibitor
For CYP450 → CYP2A9
بعض الناس شو هوه بيعمل تأثير على ادوية كتيره
من ضمنهم ال Warfarin وبعض ادوية القلب
هو دل كل الادوية Narrow therapeutic index

ال Warfarin بشو الاكل اللي بياخده ولازم ياخده؟
If you know Vitamin K dependent clotting Factor inhibitor
اذا كنت بعمل تثبيط بعمل Clotting Factor ال inhibition اللي بتتصنع بال liver
من بتصنعها؟ Vitamin (K)

طيب لو انا بعمل inhibition لهدول بدي جاي باخد من
Vitamin (K) جوا
اي أكل فيه Vitamin (K) رح يعكس شغل ال Warfarin
وبخربه ورح انو ما بخليه يشتغل
فـ رح يصيبه جلطه لانو رح يعمل [Treatment Failure]
فبيجي Second attack و Third attack
مندزه يكون في Counseling

في كمان تاني اللي هو Food
Maoinhibitor
اللي عندهم اكتئاب عنوخ ياخدو اي دواء فيه Tyramine
رح يصير لو Fatal hypertension

طيب الاكلات اللي فيها Vitamin K ← green leaves