SHEET NO. 5

PHARMACOLOGY

DOCTOR 2019 | MEDICINE | JU

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Antagonism between drugs

A. Pharmacologic antagonism

B. Physiologic Antagonist: here the drugs act independently on two different receptors and exemplified by one drug acting on the sympathetic nervous system causing the heart rate to increase and causing vasoconstriction. **HOW?** (noradrenaline (a neurotransmitter) binds to beta 1 receptor and alpha 1 receptor)

while another drug acts on the parasympathetic nervous system decreasing heart rate and causing vasodilation. **HOW?**

(acetylcholine binds to m receptors)

- if you give a patient drug A that binds to beta 1 receptors, but you want to decrease the heart rate, you should give a drug that works on the parasympathetic nervous system (M receptors).

C. Chemical antagonist: (Antagonism by neutralization): Occurs when two drugs combine with one another to form an inactive compound, and the best example being the drugs containing sulfhydryl (SH) groups, when combine with mercury or arsenic.

Enhancement of drug effects

- Enhancement = increasing the effect of a drug

A. Additive drug effect: occurs if two drugs with the same effect, when given together produce an effect that is equal in magnitude to the sum of the effect.

E AB = EA + EB 1 + 1 = 2

- If drug A decreases the blood pressure by 10, and drug B decrease the blood pressure by 10, if we give them together to a patient, the Bp will decrease by 20.

B. Synergic drug effect: occurs if two drugs with the same effect, when given together, produce an effect that is greater in magnitude than the sum of effects when the drugs are given individually.

EAB > EA + EB 1 + 1 > 2

- We never combine two drugs with the same side effects due to the synergic effect.
- To kill the cancerous cells, doctors choose drugs with different side effects.

C. Potentiation drug effect: occurs if a drug lacking an effect of its own increase the effect of a second active drug.

EAB > EA + EB 0 + 1 > 2

- For example: Parkinson patients (who have a dopamine deficiency) ---> doctors give them levodopa carbidopa. **Why?** Levodopa works by being converted to dopamine in the brain. Carbidopa (alone it has zero effect)

works by preventing levodopa from being broken down before it reaches the brain, so increases the quantity of levodopa in the bloodstream that is available to enter the brain.

Receptors are in a dynamic state

- The affinity of receptors to drugs is not fixed. It alters according to the situation.

✓ Receptor down regulation

- Prolonged use of agonist ----> decrease the number of receptors and sensitivity ----> decrease the drug effect.
  - Chronic use of salbutamol down regulates beta 2 adrenergic receptors.
  - Drug is defined as a toxic material, if you use a toxic material for a long period, your body will defend itself by decreasing the affinity toward the receptors (receptors change their 3D structure) or decreasing the signaling pathway in response to the drug.

What is tolerance?

The dose effectiveness in the beginning will not be the same when using the drug after a while (maybe one day, one year…).
So, with time, we need a higher dose to produce the same effect.

✓ Receptor up regulation

Prolonged use of antagonist ------> increase the number of receptors and sensitivity ----> drug effect?? (Doctors give the patient a drug dose more than the needed, so even though the body increase the number of receptors, there is no decrease or increase in the drug effect)

- In the patients who suffer from arrhythmia, doctors give them drugs that block beta 1 receptors.
  With time, there will be increase in the number of receptors for beta 1.
  - Propranolol is stopped after prolong use, produce withdrawal symptoms. Rise of Bp, induce of angina(ذبحة صدرية) . **HOW?**
    IMAGINE the body has 100 beta 1 receptors, with the use of this drug, the body will have 1000 receptors. Noradrenaline, in the case of 100 receptors, produces 70 heart beats. But when you stop the drug that was blocking Beta 1, noradrenaline will face 1000 receptors, produces arrythmia (140, 200 or even 400 heart beats!!) so the heart will beat very rapidly, and the result will be angina (the demand more than the supply).

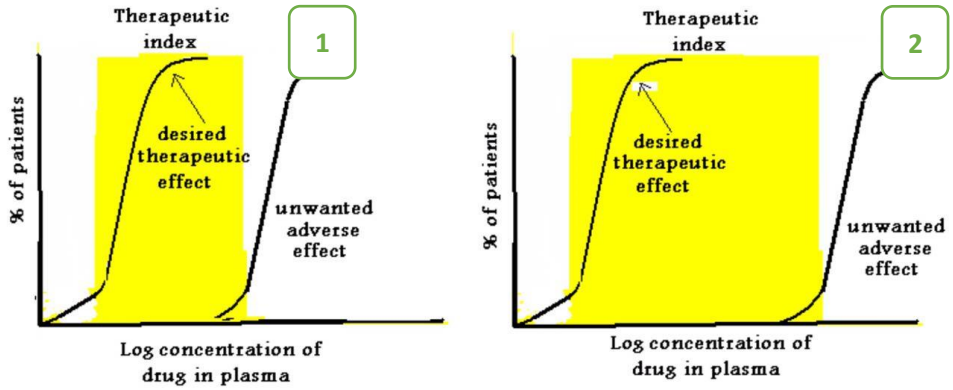
So, we shouldn't stop those drugs suddenly. we should tapper them off gradually.

Therapeutic index and margin of safety

- Therapeutic index of a drug is a ratio of the dose that produces toxicity to the dose that produces a clinically desired or effective response in a population individuals.
- Ideally the TD_{50} Should be a much higher dose than the ED_{50} so that the therapeutic index would be large.

$$TI = \frac{TD_{50}}{ED_{50}}$$

Where TD_{50} is the minimum dose that is toxic for 50% of the population, and ED_{50} is the minimum dose that is effective for 50% of the population.



According to the distance between the desired therapeutic effect and the unwanted adverse effect:

1- **Narrow therapeutic index ----> where small differences in dose may lead to serious therapeutic failures or adverse drug reactions.**

2- **Wide therapeutic index----> you have a wide range in which the drug can safely be used**

- Cyclosporine – 100-400ng/ml
- Carbamazapine- 4-10µg/ml
- Digoxin- 0.8-2ng/ml
- Phenotoin – 10-20µg/ml
- Qunindine- 2-6µg/ml

→ **The margin of safety for some drugs.**

" No one is late. Some people start earlier but end up nothing special.

Others find themselves too late, but they turn to be unique.

I know we are confused about everything. We think we are behind. But we all have different roads. Each one is made to walk it "

Unknown