◉Sheet ○Slides

number : 4

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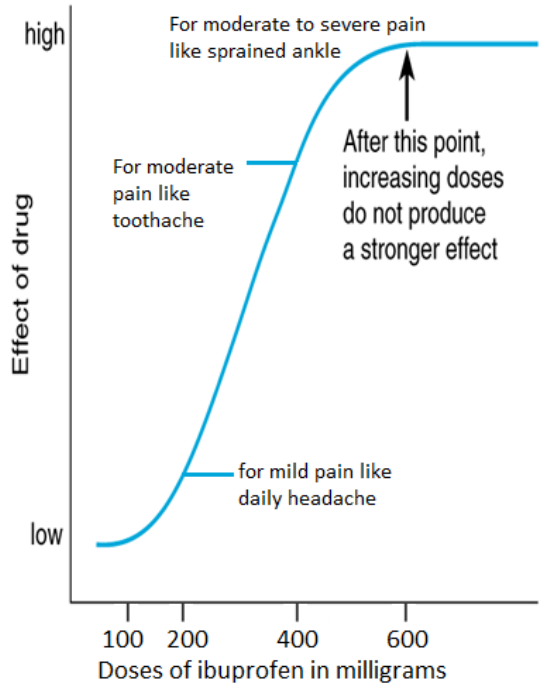
correction : moh'd abu jubba

NOTE: examples are mainly for illustration, you don't have to memorize them.

In the previous lecture, we discussed dose-response curves and here is a quick revision of them :

Dose-response curve represents the change in the effect of the dose while increasing its concentration, notice that the curve is not linear, instead it is **hyperbolic** due to many reasons such as maximization of the effect and spare receptors.
In order to make the graph easier for studying we use the [Log dose-response curve] instead of the normal curve. From the curve we know that there is an amount of drug that has no effect on the body, because the concentration of the drug is much less than the threshold, the threshold here is the minimum amount of drug that is capable of producing significant cellular events leading to therapeutic effect, These small concentrations produce **subtherapeutic** effects. As we increase the concentration of the drug above the subtherapeutic level the effect increases, so we describe the concentration of drug for patients according to their severity of illness or pain.



Example for illustrating the relation between the dose and the effect

Note that 100 mg is subtherapeutic

An important question here is “why don’t we prescribe the concentration of the maximum effect for all situations? In other words, why don’t we take 400 or 600 mg of profen for headache or any other mild pain?”
The main reason is that increasing the dose of drug is linked to an increase of **drug toxicity**, so giving unneeded amounts of drug will cause more toxicity and side effects which we can avoid by giving the exact amount needed of drug.
Another less important reason is that giving high amounts of drug will lead to **tolerance**, which is a decrease in body response towards the drug due to decreased number of the corresponding receptors (down regulation).
So always give your patient the minimal satisfying amount of drug and don’t subject him to high toxicity except in necessities.

Also, we can notice in the curve that there is a point at which the effect is not increasing anymore although we are increasing the drug concentration, which means that the drug has reached its **maximum effect** (ceiling effect or $\mathbf{E_{max}}$).
So increasing the concentration above the maximum effect concentration is not beneficial, it is harmful and causes more toxicity and side effects.
[min 00-10]

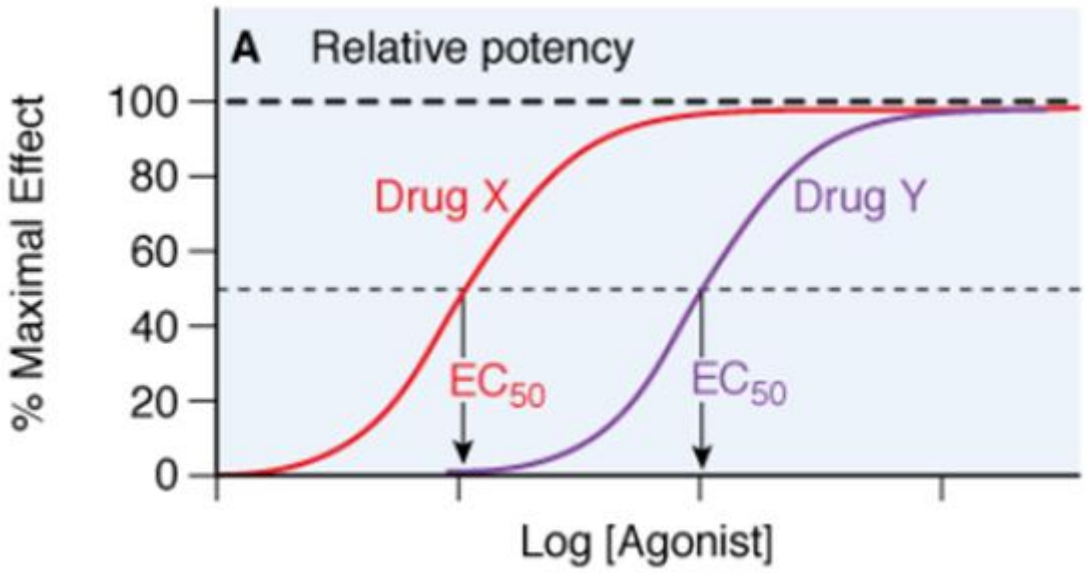
Efficacy (E_{max}) it is the maximum effect a drug can cause, it is not the same for all drugs and that depends on :

1. The number of drug-receptor complexes formed, the formation of these complexes depends on:
    a) The number of the receptors, high number of receptors will increase the chance of drug binding so the effect is increased, and vice versa.
    b) The affinity of the drug towards its receptor, high affinity will increase the speed of binding increasing the effect, and vice versa.
2. The ability of the drug (after binding) to produce an intrinsic activity compared to the endogenous ligand.

If a drug produced the same effect as the endogenous ligand it is called a **full agonist**.
If a drug produced less effect than the endogenous ligand (due to small differences in the binding form) it is called **partial agonist**.

Efficacy is important in determining which drug we should use for each situation, for example if someone has very severe pain (like cancer pain) profen - as an analgesic drug - won't be able to relieve this pain because it is higher than profen's maximum effect (profen is not efficacious enough), in this case we use a drug with **higher efficacy** like the morphine, but keep in mind that higher effect is accompanied by higher toxicity.
So drugs with the same biological activity may have different efficacies.

Potency (drug strength) is a measure of the amount of drug required to produce an effect of a given magnitude. To determine and compare potencies we use **EC50** (effective concentration 50) which is the drug concentration required to produce 50% of the drug's maximum effect.

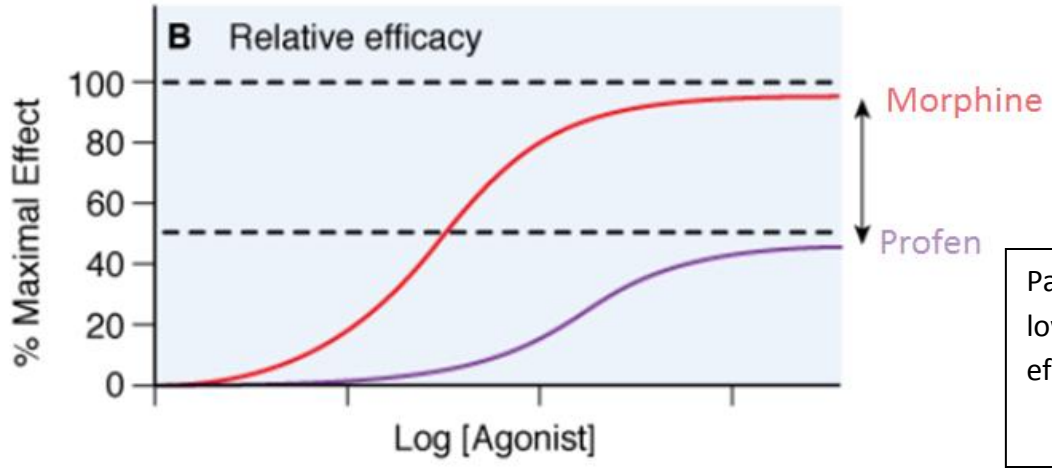


In the figure above, drug X has lower EC50 than drug Y, which means that drug X needed less concentration to reach half of E_{max} , so we say drug X is more potent.

But note that although drugs X and Y have different potencies, they both have the same efficacy, a daily life **example** of that are statins drugs, rosuvastatin has high potency and is prescribed as 10 mg, whereas atorvastatin is less potent and is prescribed as 20 mg, and simvastatin is even less potent and therefore prescribed as 40 mg, but all of them produce the same effect which is lowering cholesterol levels and they produce their effect in equal magnitudes.

The reason why drugs have different potencies is because they differ in their dissociation constants (Kd), which depend both affinity and drug concentration, so for two drugs with different potencies to have same efficacy → concentration must compensate for affinity, which means that low affinity drugs are given in higher concentrations to produce the same effect as high affinity drugs.
(For example 25 mg of volatren has almost the same effect as 200 mg of profen, the relation here is similar to the one between drugs X and Y in the previous figure)
NOTE: efficacy doesn't depend on the concentration because it only describes the effect of the drug when all of its receptors are occupied.
[min 10-25]

We also may find two drugs that differ in **both** the potency and the efficacy, an example for that is the relation between morphine, profen, and paracetamol.



Paracetamol has lower potency and efficacy than Profen

Antagonism between drugs:

Drugs may affect each other's function when administrated together.

Antagonism occurs when one drug prevents the other drug from functioning, or when one drug produces an effect that opposes the effect of the other drug,

Types of antagonism between drugs are:

1) **Pharmacologic antagonism:**

   where the two drugs have different activity on the **same receptor**, so one drug would activate the receptor and the other would inhibit the same receptor in one of these two mechanisms:

   A) Competitive antagonist: (90% of the pharmacologic antagonists)

   Here the antagonist binds noncovalently (reversibly) to the receptor, in this case the effect of the antagonist can be overcome by increasing the concentration of the agonist, so that the chance of agonist binding to the receptor is higher than it for antagonist.

   For example, adrenaline binds to β1-receprors in the heart and activates them increasing heart beating rate, to reduce the heart rate we use propranolol which inhibits β1-receptors (opposite effect, same receptor).

   In this case the [log dose-response] curve is shifted to the right, which means that we now need higher concentration of the drug (agonist) to reach half of E_{max}, because some of the receptors are occupied by the antagonist. **But** the E_{max} is not affected because the total number of receptors didn't change.

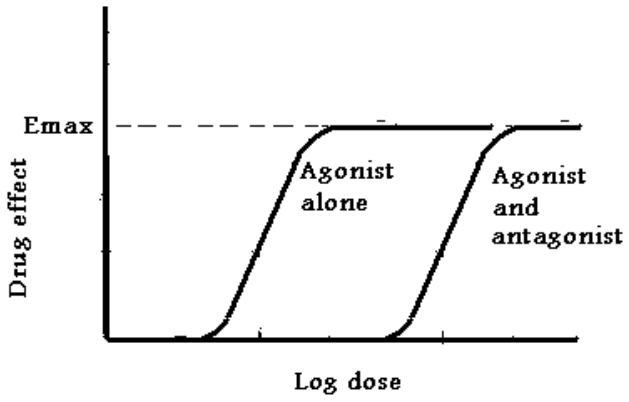


Figure showing the shift of the curve when competitive antagonist is used. E_{max} is not changed

B) Noncompetitive antagonist: Here the drug (usually a poison) binds towards the receptor **covalently** (irreversibly) at the same site where the agonist binds or at any other site on the receptor, preventing the agonist from binding to its receptor and producing effect.
In this case the reduced effect of the agonist **can't be overcome** by increasing the concentration, in other words the maximum effect is reduced because some receptors were inhibited permanently by the noncompetitive antagonists. The curve is shifted to the right and E_{max} is lowered down producing a new curve that is **nonparallel** to the old curve because number of receptors are reduced.

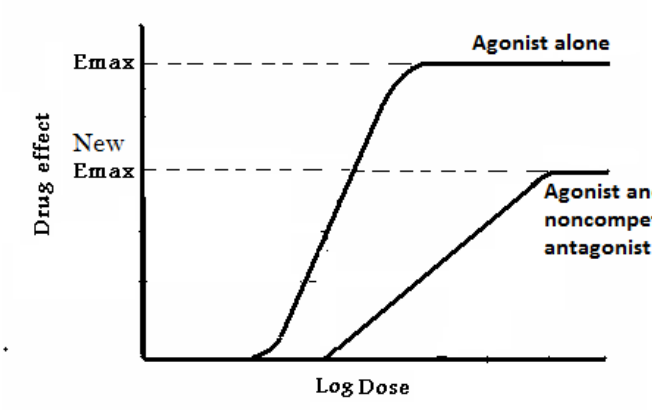


Figure showing the effect of using noncompetitive antagonist. Decreased E_{max} and shifting to the right

[min 25-35]

One way to remove the effect of noncompetitive antagonist is to wait for the body to **produce new receptors** to replace the blocked receptors. for example, aspirin has an anticoagulant effect, it binds to the platelets (cox-1 enzyme)of the blood covalently and stop their function. Therefore, a patient must stop taking aspirin and wait for 3-4 days before having a surgery, during this time the blocked platelets will be degraded and new ones will be formed.

Another way to neutralize the effect of noncompetitive receptor is using a drug that antagonises this effect physiologically…

2) **Physiological antagonism:**
   Here the two drugs have opposite effects on the body but each one binds to **different receptor**, and the binding of each drug is independent on the binding of the other drug.
   Example, if a patient has an increased heart rate due to excess drug binding to the sympathetic nervous system **covalently**, we use a drug that binds to the parasympathetic nervous system to decrease the heart rate to normal levels. (opposite effects, different receptors)
3) **Chemical antagonism:**
   In this type of antagonism drugs don't bind to their receptors, instead the agonist and the antagonist bind to each other and form an inactive compound (antagonism by neutralization).
   For example, an overdose of heparin will cause bleeding, here we use protamine sulfate which binds to heparin and stops its function.
   Another example is using antacids (like rennie) which contain $Al(OH)_3$ or $Mg(OH)_2$ to neutralize the acidity in the body.

So you should always be aware when you administrate or prescribe drugs to avoid the harmful drug-drug interactions which result from pharmacologic, physiologic, or chemical antagonism.

for example: when you have a patient with hypertension you give him a drug working on rennin angiotensin converting enzyme which work exactly on the kidney to decrease the tension but the profen and diclofinac also work on the kidney but in the opposite way to the hypertension drugs despite that every one works on a different receptor but they cause a physiological antagonism and that's why all doctors say "don't drink milk after talking a medicine" because milk contains a lot of calcium which binds to the drugs .

[min 35-45]
[Slides covered: 19-28 /lecture_1 file]

sorry for any mistakes and good luck ☺