PHARMACOLOGY

◉ Sheets ○ Slides

Number: 1

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Subject: Introduction to pharmacology

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Take a breath and get ready (:

Introduction to pharmacology

Actually pharmacology is the spirit of the medicine, and it's the relationship between doctors and patients.

We will take a lecture and a half overviewing some important points of **pharmacodynamics**, next lectures we'll take **pharmacokinetics**.

The goal of pharmacology: is to prescribe and optimize the prescription or the drug, what time should be taken, and how.

Drug naming: the examples are from Dr. Omar's slides

1- Chemical name, ex: 6-aminopenicillanic acid 2- generic name, ex: amantadine

3- Trade name

Over the counter drugs (o.t.c): simply they are drugs you can buy without a prescription, **like**: Proven, paracetamol, diclofenac, suppositories for children, anti-cough syrup…etc., all these drugs used for temperature, fever**.**

The story behind o.t.c drugs that people think that o.t.c drugs are safe & they can buy them whenever they want, but actually o.t.c drugs are **NOT SAFE**.

Doctor mentioned a small story about o.t.c drugs:

A patient has a dental pain, his mother gave him (**Revanin**) drug which is an o.c.t drug, when he came to the university, the pain didn't go; so he asked his friend who gave him another drug called (**Panadol**).after 2 to 3 hours, the pain still on the teeth of this patient who still suffering from the pain, he found another student who gave him another drug called (**Lemsip**). Then he went back home, his mother asked him whether he's pain relieved or not, he replied: not yet; so she gave him another drug called (**Tylol**), then he went back to the pharmacy, the pharmacy wasn't a good one and gave (**Panadol extra**) but actually, the dental pain was moderate, and does not response to any of previous drugs, the **shocking part** was that these 5 drugs are the same drug. So; this guy ended up with liver toxicity, and he came with a pain to the emergency room and he had an acute liver toxicity because he took too much of paracetamol.

But why we don't really know they are the same drug??? Simply because they are being sold in trade names and over the counter.

The question is: is this incidence common or unique?

It's **common**, you have to understand that the safest drug is paracetamol, the generic name, but the most commonly acquired toxicity comes from the same drug paracetamol.

All this story comes from a problem in:

1- **NAMING.** → Do NOT use trade names 2- Thinking that o.t.c drugs are safe.

Another simple story about this problem.

A lady has 5 so on-fire children (active all the time), she went to the pharmacist and told him give me a drug for headache *_* he gave her **Advil** or **Profen** without a prescription, this lady went back home and relieved from pain until 5th day becoming used to the drug, she went to the pharmacy next week buyin the drug itself without asking the pharmacist because this drug relieves her pain and took Profen daily → she ended up with **kidney failure.**

As we see this problem comes from **lacking of knowledge as people think that o.t.c drugs are safe.**

Also, some o.t.c drugs such as Diclofenac, profen and voltarine antagonize anti-hypertensive drugs, so if a patient with hypertension took those drugs there will antagonism → blood pressure will raise because of using these drugs more than 5 days let's say.

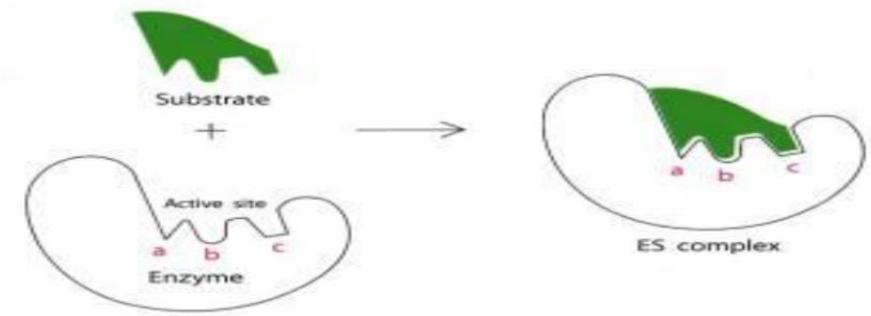
But who will tell this 60-year-old patient that those drugs are not safe??

No one because those drugs are o.t.c and pharmacist doesn't know to whom this drug is given

Note: remember to ask your patient if he has taken o.c.t drugs or not, they are not safe drugs & don't exclude them from the history of the patient.

Model of drug/receptor binding

99% of drugs that prescribed to the patient go toward the body and find the receptor then produce **therapeutic effect**, the rest 1% don't use receptors we'll take them later.



We've a drug and receptor/enzyme (whatever the receptor), we need to understand two things before we take the pharmacological ideas:

1-FIRST: comes from biochemistry that tells you that receptors in the body made up of amino acids, and most of the receptors in the body have proteins, they have something called **homology**.

Homology: receptors look like, for ex: alpha1 receptor looks like alpha2, beta1 receptor has some similarities to beta2.

Binding of the drug toward the receptor depends on **Affinity.**

If I'm targeting my drug toward beta1 receptors, it's going to bind beta1 mostly, but this drug will also bind -a little extent- beta2 receptors, but **why** this drug will bind beta2 for a little extent?

Because beta2 receptors have some homology toward beta1→this is the first story of **side effects**

There's no drug with a single effect, so; my drug will bind other receptors also→side effects

The drug is selective but NOT very specific, it has some selectivity but nothing promotes 100% selectivity may be 90-94% selectivity.

So I'm targeting beta1, drug mostly binds beta1, little extent binds with beta2, less extent binds with alpha1- because alpha1 also has less homology to beta1- so on and so forth.

2-second: comes from physiology, same effector will bind at different sites on the body→we'll have different activities (The same receptor is found in different tissue, and in each place it has specific action), beta2 will bronchodilate muscles of bronchi, at the same time it will work on glucose metabolism, so if I want to bronchodilate my patient I'm going to affect his glucose metabolism, WHY? Because beta2 is present in lungs, liver, aorta and other parts of the body.

And at every single part this beta2 has different activity, and this will produces side effects.

Note: when side effects are bad then they will be called **Adverse Effects**

To sum up: side effects are either from biochemistric reason: homology of receptors→drug binds with other receptors in little extent, or from physiologic reason: same type receptor is present in more than one tissue → drug binds its receptor→different activities (side effect).

Major receptor families

We'll overview them please refer to lippincot page 27

1-Ligand-gated ion channels:

- Acetylcholine will bind nicotinic receptor producing action potential then muscle contraction.
- Calcium channel blocker drugs, Ca channels have binding sites, my drug will go there and blocks them→ I will reduce the amount of calcium going through the cells →reduce contractibility –relaxation- so; I can use Ca channels blockers as muscle relaxant or anti-hypertensive drugs .

2- G protein-coupled receptors: alpha 1&2, beta 1&2 receptors are G protein-coupled, effector→subunits of g protein→ second messenger

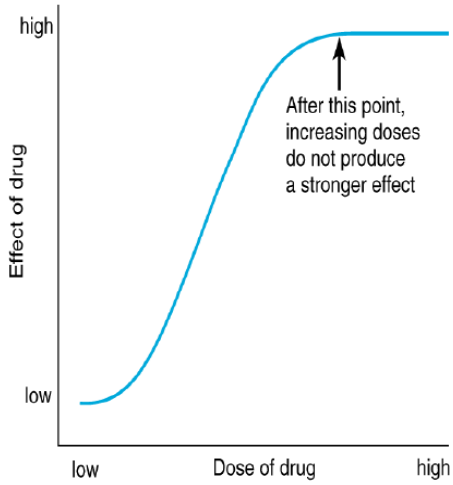
3- enzyme-linked receptors: the common example is insulin.

Insulin binds with its receptor→phosphorylates tyrosine kinase →sequence of reactions →therapeutic activity.

4- Intracellular activities: mostly for steroids**.**

Steroids cross plasma membrane → binds intracellular receptors inside the cell→ carrying to DNA→ producing different gene expressions

Graduated dose/response curve –important medically-



First I give drug with low conc. Then I gain low response, and as I increase the conc. Of my drug, I gain more effect **until** I reach the max effect so I have:

Lag phase: I give the drug but the patient does not respond. (Here we call it sub-therapeutic effect)

I increase the dose, the effectiveness is increasing until I reach **saturation-**pointed at diagram**-** where there are no more receptors to occupy, so; I should not ever get more drug more than this-saturation- because all receptors are already occupied, and if I get drugs more than this the drug that didn't find sites for binding is now free → it will bind with less affinity receptors→ side effects will appear more clear as I'm increasing the drugs, **why?**

Because the amount of the receptors is going to be less than the amount of free drug-unbound drugs- and those drugs will go through blood to homologal structures and bind to them occupying different receptors producing different activities, **don't give drugs over the ceiling effect (E_{max}) to avoid side effects.**

To understand more when you go to the pharmacy you will find profen with 200mg, 400mg and 600mg conc. and you will not find 100mg profen because it will not produce any effect.

Why is there many conc. Of profen ?

Because that patient represents himself to you as a doctor with different levels of pain, some of them might have **mild** pain, **moderate** pain, or moderate to **severe** pain.

Patient with mild pain→ we give him 200mg

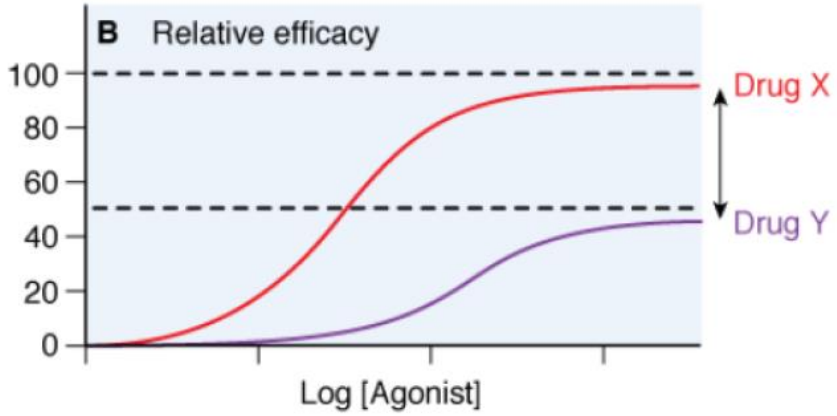
Moderate pain like: toothache→ 400mg note: paracetamol's E_{max} is at mild pain not moderate so it can't relieve a tooth pain.

Patient with moderate to severe pain like: rheumatic arthritis →600mg

Now the **<u>question</u>** is: why don't we prescribe 600mg profen from the beginning for all patients with all levels of pain???

Simply, if we increase the dose, free drug will be a lot, side effects will be subsequently a lot. So you don’t have to have side effects unless there is a reason.

Now we will explain why paracetamol does not really treat dental pain which is a moderate pain.



Drug X = profen

Drug Y= paracetamol

As we see above, paracetamol is less efficacious (or has less efficacy or has less E_{max}) than profen, thus whatever the quantity you give the patient it will not give a response for treating dental pain in addition that the patient will get a liver toxicity as mentioned earlier.

Mostly we choose the drug according to its efficacy.

Another clear example:

A patient has cancer pain we can't give him profen because it will not give a response even if I give him 600mg, 1200mg, or 1500mg **why?** Because the pain of the cancer is much higher than E_{max} of profen –same story of paracetamol- it will not reach it, so for treating the pain of cancer we use **Morphine** which has a very high E_{max}.

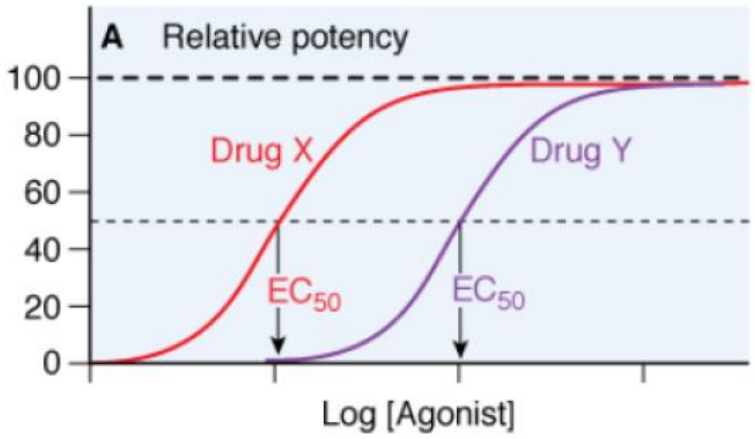
Note: the only open E_{max} is belonging to morphine, as you increase the dose, you get more effect, and the only problem with it is that the toxicity produced from it can kill the patient, but it has a high efficacy. (So whenever the patient has type of severe pain we go to something called **Apioles)**

To sum up: different drugs have different efficacy E_{max}, increasing the dose does not guarantee that you're taking more effect because we reached the plateau E_{max}

Now we've known about efficacy, we will talk about something called **Potency**

Actually what we are interested in as doctors is efficacy not potency, potency is important to pharmacists :p **why?** To be able to determine the amount of the drug a patient needs.

An example for more explanation.



Drug X= diclofenac or voltarine

Dug Y= profen

Diclofenac has same E_{max} of profen's but different potency.

The amounts of drug for voltarine are 50, 75 & 100mg , simply that means that 50mg of voltarine produce same effect-relieving mild pain- of 200mg of profen, 75mg voltarine equivalent to 400mg profen that both of them treat moderate pain and 100mg voltarine is also equivalent to 600mg profen.

At the end of the day, we're going to reach similar efficacy and they cannot treat cancer pain.

To sum up: those 2 dugs have different potency, diclofenac or voltaine is stronger than profen **in the amount level NOT efficacy**. Efficacy: magnitude of respose, potency: amount of drug producing response

We mean that we need little amount of diclofenac to produce the same effect of large amount of profen, so don't care to the amount even it's large, ex: 1000mg of paracetamol = 200mg of profen = 50mg of diclofenac.--> they have different potency.

At the end of the day profen and diclofenac will reach the same E_{max} but paracetamol not as we mentioned previously.

EC_{50}: the dose that will produce a 50% effect for the patient**.** It's used to determine the potency of drug.

We've hundred patients we gave them different doses, the dose that will produce an effect in 50% of dose patient we will call it **effective dose 50** or **effective conc. 50.**

Again as doctors we don't need to deal with potency or EC_{50}, but pharmacist do need to calculate the amount of drug will give to the patient, we really are interested in efficacy not much in potency.

Agonist and antagonist

Agonism: to bind a drug toward the receptor and **activate** it I will call this (drug/endogenous material) **agonist**.

Antagonism: simply when an antagonist binds its receptor, all what it does is just **blocking** (preventing) endogenous material to bind the receptor.

99% cases drug will bind the receptor preventing agonist from binding to the receptor.

What is the original agonist that presents in our body? It is the endogenous material, because all receptor in our body must have original agonist, and this is from the wisdom of Allah.

In pharma our task is either to enhance the agonist-endogenous material- or block it.

For example: when you are standing adrenaline binds beta1 receptors giving you some sympathetic activation, if I want to increase beta1 activity I give a drug that is similar to adrenaline,→1- it will bind also to beta1 receptor 2- there will activation for adrenaline activity but **how? 2 methods**

1-There's a time when the receptor will be free, and when I give an agonist I occupy this time, in other words adrenaline usually is going to bind and come out the bind and come out subsequently, this time for coming out the drug that I give it for the patient to enhance will occupy that time→ I'm giving agonism and activating endogenous material for the activity.

2-There are also different types will bind in more affinity toward the receptor than adrenaline so if there are more agonist of this type than adrenaline, I give more effect.

So antagonism is the time when a drug occupies the receptor and prevents binding and coming out of adrenaline.

This is the relationship between the endogenous material and the drug.

A similar relationship present between drugs, if a drug A that binds to beta1 & a drug B that also binds to beta1→ they will do either enhancement for each other- **competitive agonism**- OR antagonism **-competitive antagonism-**

This important relationship between drugs we use it a lot **where?**

In **treatment**, if the patient is overdosed by a drug, I will give him another drug that antagonizes the first drug this is called→ **toxicology** or **treatment of overdose.**

And vice versa if a drug is giving a little effect and I want to enhance it I will give him agonist.

Is agonism/antagonism only happening through pharmacology or receptor?

Of course NO, there's something called physiological antagonism and something called chemical antagonism.

Physiological antagonism: if someone is standing-movement- the sympathetic activity is more than parasympathetic one and vice versa if someone sitting - digestion- the parasympathetic effect is more than sympathetic one, → we live in a balance.

Another example we will take it in CNS is the movement of the brain depends on acetylcholine & dopamine; any disturbance on the balance between them→ruined movement -no normal movement-

Can I produce antagonism through affecting the physiological activity? YES, by increasing parasympathetic and sympathetic activities which both opposite each other originally.

Ex: I give drug A that activates parasympathetic, and drug B that activates sympathetic→I activates sympathetic and parasympathetic→increase antagonism.

Same concept, if I give a patient a drug that activates parasympathetic and a drug inactivates sympathetic→ increase agonism.

Beta2 receptors → dilation, muscarinic receptors M_2 → constriction

When I want to dilates the bronchi, I give beta2 agonist and M_2 antagonist.

Chemical antagonism: mostly happening though **antidotes** (مضاد سمية) : drugs that go towards other drugs & bind to them then render their activity or decrease their activity **how?**

When snakes bite they inject venoms-poison-, and let's consider this venom is a drug this poison will produce an effect not a therapeutic one but toxicological effect, **what** I have to do? I will give antidote-fab- which is made of antibodies that will go to the venom binding to it then render its activity.

In hospitals we've a drug called **digoxin** which is a toxic drug, whenever It raises in patient's body→ I give him an antidote also it's fab but different fab – more antibodies- that will bind to digoxin and reduce its activity.

The common used chemical antagonist is **antacids,** like: Maalox, antacids are bases with acids of stomach→ neutralizing PH of the stomach.

Enhancement of drug effects

It comes from the same story of antagonism but now we have enhancement.

1- Additive drug effect-additive agonism: $E_{AB}= E_A+E_B$

For example: you have a drug A that has a magnitude effect of 10, and drug B of a magnitude effect of 10, then: $E_{AB}=20$

2- Synergic drug effect-synergism: $E_{AB}> E_A+E_B$

Synergism: exaggeration (تفاعل شديد), which is a strong reaction with drugs not between them. Ex: $E_A=10$, $E_B=10$→ $E_{AB}=50$

Synergism is very important in medicine because whenever you give 2 drugs together, we don't really have an additive activity, in many cases we have synergistic activity -the body will respond with more summation of 2 drugs - it's important when we'll take antihypertensive drugs.

3- Potentiation drug effect: will be explained next lecture.

Thank you for reading, and I'm sorry for any mistake ☺