PHARMACOLOGY

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Number: Sheet 5

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Subject: Steady State and Adverse Effects

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Last lecture we were talking about the steady state and today we are going to complete this topic.

we know that the steady state is a state where the rate of administration of the drug = the rate of its elimination, and we reach it after 4 or 5 half-lives from the first administration of the drug .

we always want to reach the steady state to have a constant concentration of the drug in the patient's body to protect him against any event and to treat him, and if the drug's concentration is decreased below the steady state this is a big concern.

But if we have a drug with a short half-life (let's say 2 hours), it's not an option to give the patient a dose every 2 hours (12 doses a day).

- So what we can do to overcome this problem?

1-**sustaind release drugs**: this way deals with the formulation of the drug, we can mix the drug with other substances that makes the drug a sustained release drug resulting in increasing the half-life.

But what if we can't make the drug a sustained release one .we will move to:

2-**potentiation**: give another drug without any effect just to make the half-life of the original drug longer.

3-**increase the dose**: If we increase the dose to compensate the short half-life we will have a much higher fluctuation. (So we will have a dose higher than the therapeutic dose so when it decreases after a while it will still be effective) .But this way can't be applied for any drug , it is only applied to the drugs with a **wide therapeutic** index , so if its applied to a narrow therapeutic index drug we will touch the toxicity.

- This way is mainly applied in the antibiotics and flurosemides (one of its trade names is lasix), lasix is a diuretic drug, it has a short half-life (2 hours), but we give it 3 times a day by giving a higher dose as it has a wide therapeutic index.

****But** if we have a drug with a short half-life and **a narrow therapeutic index**:

We can only give it by infusion using a drip that has a regulator, so we can control the administration and elimination of the drug. When the administrated amount of the drug is small, the fluctuation is small. So we should not give a dose and wait for the drug amount to decrease, we should give continuous small doses, so whenever the concentration of the drug is decreased, we are compensating this drop in the drug's concentration, until reaching the steady state (plateau). And the time needed for that depends on the rate of administration.

that is why some drugs are not given except in hospitals, there are no oral forms of them only injectable forms.

NOTE: when the doctor explained this topic, he meant by the concentration of the drug the concentration that is **in the blood.**

Q: why not all drugs can be taken orally?

1- The drug can't be absorbed.
2- The drug has a lot of first pass metabolism so none of it is reaching the circulation.
3- The drug has a very low half-life and a narrow therapeutic index.

First two conditions can be solved by either taking the drug sublingually or as a suppository. The third condition has only one solution, which is by infusion.

Summary:

- The oral drugs are usually given every half-life and eventually they will reach the steady stare with an acceptable fluctuation because they have a **wide therapeutic index** and **relatively a long half-life**.
- Drugs with a short half-life and a **narrow** therapeutic index, we give them **by infusion** in order to reach the steady state without fluctuation.
- Drugs with a **short half-life** and a wide **therapeutic index**: we can increase the dose (but remember we fluctuate above the sub-therapeutic level and below the toxicity).

- In order to reach the steady state we need a 4 or 5 half-lives as we said before.
- Now if the patient missed some doses, this means we are destroying the steady state that we built. So.. we need more time to reach the steady state again, and so on each time the patient misses a dose or more, the patient will always be below the therapeutic level and the drug will not have an impact.
- This happens a lot with patients, especially when taking antibiotics and diabetic drugs. And this is related to the mentality of the patient which is so important in the medicine field so we need (us as doctors) to understand the patient's psychology.
- so when a patient misses a dose the drug concentration is going to be below the steady state(under the desired therapeutic level) , and we will need another 3 or 4 half-lives in this case to reach the steady state again and so on so forth. And sometimes the drug ends with no effect.
- This is related to the adherence, we must convince the patient to adhere to the drug. Because if not, the treatment will fail, and the patient will blame the doctor.

- **NOTE:** before reaching the steady state we are increasing the concentration of the drug in the body until we reach the desired dose which is the steady state, then the concentration of the drug will be constant.
- **NOTE:** the dose we give to the patient is not the same for all patients, we don't dose them haphazardly, and it is calculated for each. These calculations depend on:
  1- clearance
  2- accumulation factor
  3- volume of distribution
  4- Half-life

These calculation are complicated, and we are not supposed to know them, we need to understand the concept only.

REMEMBER: that all of the explanations regarding the steady state until now is applied only to the **first** order reactions.

- Again, reaching the steady state ⟶ less fluctuation ⟶ less side effects.
- To **stop** the drug we also need 4 or 5 half-lives for the drug to be eliminated:

We treat it as a single dose. If we gave a patient a single dose it needs a 4 or 5 half-lives to be eliminated.

EX: if we dose a patient a single dose (100mg), it will be decreased to 50 ⟶ 25 ⟶ 12.5 ⟶ 6 ⟶ 3 and the rest of the drug is neglected (we don't count them). **So we need 4 or 5 half-lives**. This is important in surgeries, because some drugs must be totally eliminated from the body before the surgery. In this case we must stop the administration of the drug before the surgery 4 or 5 half-lives.

- The last point: if we want to reach the steady state **immediately**. And we can't wait 4 or 5 half-lives. This is not going to work as some drugs have a long half-life (1 day for example or 3 days). So we give the patient a **loading dose** (a high dose) then we dose him with the normal dose each half-life or the frequency that we want. Even if the drug has a narrow therapeutic index we dose him a loading dose within the therapeutic range to make sure that we got the targeted concentration that we want.
- The **loading dose**: is a high single dose we give to overcome the time needed to reach the steady state (4 half-lives), we will overcome the time needed for accumulation .So if there is a patient who needs an immediate surgery we dose him a loading dose and then a maintenance dose.

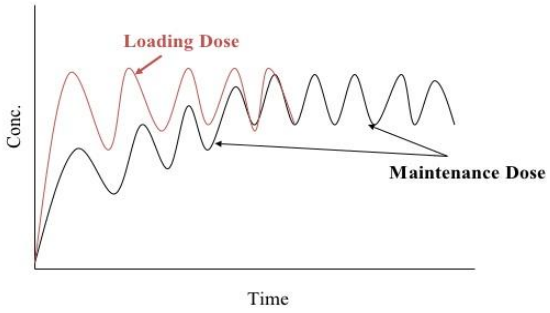
EX: a patient is going to have an angioplasty (قسطرة), we will put a stent in his vessels, this will cause an injury in these vessels leading to coagulation. So we need to give him an anticoagulant drug.

And instead of waiting 3 or 4 days to make sure that the drug has reached the steady state, we give him directly after finishing the surgery a loading dose. SO instead of giving the patient a 75mg dose of an anticoagulant drug, we give him 600mg dose that will increase the drug concentration quickly and then reach the steady state. Then we give him the maintenance dose which is 75mg, after a while the doses (loading and maintenance) will reach the **same point which is the steady state.**

- The aim of the **loading dose** is reaching the steady state **quickly.**
- We give a loading dose then a maintenance dose.
- We use the loading dose when needed. We don't use it with the normal patients.

NOTE: we can also give a loading dose orally.

IV Loading Dose & Maintenance Dose



❖ Drug – drug interaction :

- The doctor told us to go through the slides by ourselves (because we already talked about drug-drug interactions in the previous lectures) but he mentioned some points about it.
- Drug – drug interaction happens at these sites:
  1- Site of action: drug antagonism
  2- Absorption: tetracycline is not absorbed if calcium product is present in the stomach.
  3- Metabolism or biotransformation (by CYP450)
  4- Drug distribution: aspirin compete with methotrexate for protein binding sites, because aspirin is more competitive for these sites, resulting in an increased release of methotrexate which will increase toxicity.
  5- Execration: digoxin and quinidine are both excreted from the same site in the kidney. The quinidine will be excreted first because it is more competitive for these sites, resulting in increased serum levels of digoxin.

❖Adverse effects :

- NO DRUG PRDUCES A SINGLE EFFECT !!
- The difference between side effects and adverse effects:
  The side effect: any effect of the drug beside the therapeutic effect. It may be good or bad.
  The adverse effect: undesired effect that may be unpleasant or even dangerous, that can occur for many reasons.

- **Causes of adverse effects:**

  1- The drug may have another effect beside the therapeutic effect. WHY?

  Because of the physiology and biochemistry of our body:
  -The physiological point: the receptors of the drugs are found in different sites in the body producing different effects. Some of these effects are going to be adverse.
  -The biochemistry point: **Homology,** the drug will bind to the receptor we want and other receptors as well because there isn't such thing as **absolute** selectivity in pharmacology, it is a **relative** selectivity.

  2- The patient is sensitive to the drug**:** his body recognizes the drug as a foreign material resulting in allergy.

- Every human has some kind of allergy towards something.
  EX: some people have an allergy towards Penicillin: when penicillin is metabolized, it will produce another compound that will bind a protein. The resulting complex is an antigenic complex called "haptin". People who are allergic to Penicillin, their body will recognize haptin as a foreign material which results in an allergic reaction caused by the immune system, when the immune system is activated Histamine will be secreted in this case, causing bronchoconstriction and vasodilation (which will decrease the blood pressure). This is called anaphylactic shock, It is treated by adrenaline because it binds to beta 2 receptors and cause bronchodilation and it will also bind to beta 1 receptors and cause an increase in blood pressure.
  -Some people have an allergy towards diclofenac (voltaren). Some people have an allergy towards sulfur-containing drugs. Some people are allergic to hay (hay fever).

  3- The patient is taking:

- **Too much** of the drug (approaching the toxicity level)
- Or taking **too little,** and this happens only in one case: taking a low amount of antibiotics (sub-therapeutic level). This will kill the good bacteria in the body and it won't affect the bad resistant ones.

Leading to a state called superinfection in which we allow the bad bacteria in the body to grow instead of the good bacteria.

- **EX:** clostridium difficile bacteria are a type of bacteria in our body that is resistant to all types of antibiotics. When taking a low amount of an antibiotic the good bacteria in the body will die which usually compete with clostridium difficile. This will allow the clostridium difficile bacteria to grow causing a pseudomembranous colitis.
- **NOTE:** One of the most opportunistic micro-organisms in our body is the clostridium difficile.
- **NOTE:** the number of the bacteria in our body is larger than the number of our cells.

• Types of adverse effects:

1- **Type A**- exaggerated pharmacological response:

Some people (1 or 2 out of 100) when given a drug, they exaggerate the side effects. (their body is sensitive for the drug, their pathophysiology is different)

Ex\ Bronchospasm from beta blockers, because some patients may have more beta2 receptors.

Ex\ Some people (1\1000) may develop toxicity from a drug called aminoglycosides, and it will result in deafness, so they may lose their ability to hear because of this drug, due to some pharmacological reactions producing toxicity in their body.

This actually is not well understood scientifically, but it exists. For example if you have 100 patient with the same levels of the metabolism and activity of CYP450 and other kinetic parameters. And you dose them with a normal dose of the drug; some of them will have side effects. This is called **exaggeration.**

Another EX: some people when taking asthma drugs like salbutamol which is a beta2 agonist (it works on the lungs), some of the drug will bind to beta1 (no absolute selectivity) causing palpitation (only 4-5% of the people).
And that's because they exaggerated the response of the drug, they have too much active beta1 receptors.

2- **Type B**- Nonpharmacological:

- ❖ It's not related to pharmacodynamics.
- ❖ And it's not related to the number of the receptors.

- Often an allergic response, like the penicillin.

3- **Type C**- continuous or long term use:

- Sometimes the side effects are observed after a period of time from taking the drug (time related side effects). So the side effects need a continuous using for a long time to appear.
- EX: menopause women usually take steroids as the estrogen levels decreases at this age, so one of the side effects is that after 6 months of taking estrogen she may suffer from osteoporosis.
- EX: cancer drug induce leukemia: a woman for example suffering from a breast cancer, she may suffer after 3 years from leukemia.

4- **Type D**- delayed (lag time) :

- I use the drug today, and I get the side effects after 3-5 years.
- This type is rare.
- Like the teratogenic effect. EX: a woman had a cancer and was cured, she got pregnant and she delivered a baby with a congenital malformation because of the cancer treatment even it was maybe 5 years ago. And that's because anticancer drugs (chemotherapy) affects the ovaries.

5- **Type E**-ending of use (withdrawal) :

If we stopped the drug, we will have the side effect. **EX:** normally the steroids are synthesized within our body. If a patient is taking cortisone, he is gaining steroids from an exogenous source, so the site for steroid synthesis (adrenal cortex) will undergo atrophy. And the body will depend on the exogenous steroids. If we stopped cortisone suddenly this will result in withdrawal symptoms and adrenal crisis because there are no steroids in the body. And the body is not going to work properly without steroids.

EX: a sudden stop in a beta blocker drug, will cause binding of the adrenalin to beta receptors so strongly (it will bind in high affinity and also the number of the receptors may be higher than usual because of the up regulation) causing angina and arrhythmia.

NOTE: the side effects (the withdrawal symptoms) of this type will be observed after 4 or 5 half-lives after stopping the drug (when it's fully eliminated from the body). But sometimes after 2 half-lives only because the drug will be under the sub-therapeutic level.

- So we avoid these withdrawal effects by **tapering** (decreasing the dose **gradually)**.

- EX: some surgeries require a decrease in the immunity of the patient, so we give him cortisone for 6 months before the surgery to achieve that (the cortisone is related to decreasing the immunity). And when we want to stop cortisone it takes 4 months of decreasing the dose to prevent the side effects and prepare the body to synthesis cortisone as before.

6- **Type F**-failure of efficacy :

The continuous use of the drug may result in a failure of efficacy. This is related to **tolerance**, ex: the patients who take an overdose of heroin, the body is not responding to heroin because the heroin has already reached its maximum efficacy.

EX: the same will happen if the patient is taking a lot of antibiotics; the body will be full of resistant microbes. The antibiotics will have no effect. This is why (75-90)% of antibiotics are not effective and no longer used.

EX: the loss of effect for the hypnotic drugs

❖ **NOTES:**

- In general the maximum time needed to make sure that there are no side effects of any type depends on the drug :
  - For example: some women in Iraq still born babies with malformations and leukemia!
  - Ex\ women must stop vitamin A drugs 3 months before pregnancy.
- The patient must know about the side effects before we prescribe the drug. for example: we use for the treatment of breast cancer a drug called tamoxifen, but this drug may cause endometrial cancer after a while of stopping it (the possibility is 1%) so the woman must know about that and agree to it .They have to sign . On the other hand we as doctors are not allowed to use this drug more than 5 years, because the possibility for the endometrial cancer to happen will increase from 1% to (2-6)%.
- Note: there are side effects does not belong to any of the types mentioned. These side effect are psychological effects called **placebo** effect, they are related to the psychology of the patient not the drug or the receptor. So a patient may create a side effect that is not really existed!

Sorry for any mistakes …

Wish you all the best

STUDY HARD!!