Medical Committee
The University of Jordan

PHARMACOLOGY

Lecture No.: 6

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SLIDES

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Drug Accumulation

-Drug accumulation: a condition that occurs after repeated drug administration . This means that if the dosing interval is shorter than four half-lives , accumulation will be detectable.

For Example: when you prescribe a drug, you ask the patient to take it 1-4 times daily, and with this repeated administration(repeated doses), drugs will accumulate IF they are administered by time interval less than 4 half-lives.

Why 4 half- lives?

As we know, approximately 95% of the drug will disappear from the body by the time it reaches 4 half-lives, and thus there will be no accumulation. But if we give a new dose in less than 4 half-lives, some drug will be left, and doses will build on each other.

-Dosing interval : time between doses. (for example: if you give the dose every 6 hrs ; dosing interval is 6 hrs, if you give it every 12 hrs, the dosing interval is 12 hrs, and so on.)

-Drug accumulation is inversely proportional to the fraction of the dose lost in each dosing interval. (The **more** the loss of the drug, the **less** the accumulation, and vice versa).

Accumulation factor: 1/ fraction of drug lost in one dosing interval or 1/1- Fraction remaining

Q: Suppose we are giving a drug every 1 half-life, what is the fraction lost?.

A: 50%.

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Q: What is the accumulation factor if there was repeated administration every half-life?.

A: 1/0.5 = 2.

-Why should we worry about this (what's the benefit of accumulation factor)? To predict the concentration of drug after repeated administration compared to the concentration after the 1st dose (the ratio). Why? So that we can know the steady-state concentration.

- Example: if we have a peak concentration of 10 mg/L after the first dose, and the peak concentration after repeated dose at the first half life which is the steady state(for example) is 20 mg/L, because the accumulation factor is 2 as we said previously for the first half life. We multiplied the peak concentration after the first dose (10) by the accumulation factor (2) to get the peak concentration at steady state.

-In other words: I give a dose, I measure the concentration after one dose, then I can say : because the accumulation factor at this dosing interval was so and so, I expect the steady state to have that concentration.(prediction)

Why do we need to know the steady state concentration? Because the therapeutic effects of drugs take place at this concentration.

-Steady state: when the rate of drug administration = the rate of drug elimination.

Rate of administration : frequency of administration (example: 100mg/ 6 hrs, which also means 400mg/24 hrs, or you can give 500mg/6hrs which means 2g/day..etc..)

*When rate of administration = rate of elimination drug concentration will be steady/stable.

So the accumulation factor predicts when to give the dose (once every half life or once in every 2 half lives) by knowing the fraction remaining after the first dose I predict the concentration at steady state and give accordingly specific doses intervals. Because we want to give the exact therapeutic concentration not toxic nor subtherapeutic ones.

The summary:

Peak conc. at steady state = peak conc. After 1st dose x accumulation factor

Or we can measure the trough concentration which is the dip (opp of peak)

If we're asked about the **trough** concentration:

trough conc. at steady state = trough conc. After 1st dose x accumulation factor

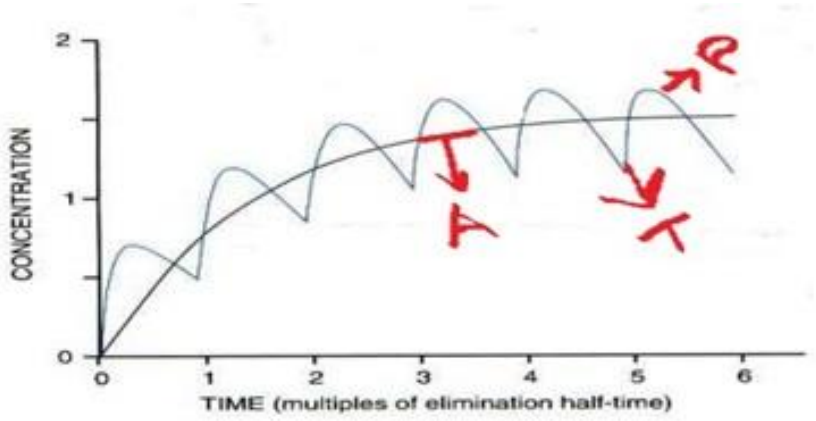
Same thing with **average** concentration..

Avg conc. at steady state = Avg conc. After 1st dose x accumulation factor

-At steady state, constant peak, trough, and average concentrations are achieved. (the figure)

***Note: average is <u>not equal to</u> (peak+trough)/ 2. It has specific calculations.**

Take a look at the figure: Peak (P) / Average (A) / Trough (T)



The steady state will be achieved after 4 half-lives.

Q: why?

A: after the 1st half-life: 50% remains, and after the 2nd half-life : 75% remains , after the 3rd half-life : 87.5 remaining , and after the 4th half-life : 94% remaining, so the steady state is achieved after 4 half-lives.

-This drug is administered every half-life, when the first dose (1g) drops to one half (1st half-life) you give the second dose, so this new dose is added to half of the remaining dose(the previous dose), now we have 1.5 g,(0.5g remained from the first dose and 1g is the new dose), now when another half-life passes we have 0.75g, we add another dose(1g): 1.75g , and after 3rd half-life we have 1.875g, and after that 1.94g (approx. 2 times the concentration after the first dose which indicates the accumulation factor is 2 as we said). So we can predict the peak concentration at the steady state from the first dose. (the previous figure)

- You can try it at home and draw a graph, put any concentrations and the time in half-lives and you'll end up with a figure just like above.

-Again, the peak, the trough , and the average drug concentrations must be in the **therapeutic range.**

-Therapeutic range: the range between the minimal effective concentration (MEC) and the minimal toxic concentration (MTC) (check the figure on the slides).

-Our aim is to reach the steady state within the therapeutic range.(you give a patient a drug that reaches the steady state after 4 half-lives, and this steady state has to be therapeutic, it has to be within the therapeutic range). Means that we must check the peak, trough and average concentrations.

-If a mistake occurs, you may have a steady state, but not within the therapeutic range (sub-therapeutic for example –under the MEC line in the figure-), or toxic (above the MTC line.)

Q: Are the first 2 doses with no effect?

A: In this case (the previous figure), the 1st dose is with no effect, the 2nd dose has only a little effect, and the 3rd dose has more effect.. but it doesn't apply for all cases. Each case is different but generally drugs take some time to be effective.

Q: Why do we give it after 4 half-lives?

A: because the concentration after 4 half-lives will be 1.94 which is approximately 2, and that's when the steady state is accomplished, 5% or 6% is not a significant difference here.(6.25% the amount that remains of the single dose after 4 half- lives)

Note: Unless a physiological change happens, the steady state will continue as long as you give the right dose at the right frequency. Assuming that it's first order elimination kinetics.

Q: Can we calculate the accumulation factor from the graph? Yes. But as a doctor you have to predict it in order to prescribe the correct dose without the need of the figure.

Now take a look at the two graphs on the slides:

*The graph on the **left:**

It's a graph of a certain drug, given at a certain interval, and it follows first order kinetics (not normal kinetics as the slide shows because both zero order and first order are normal!!)

-We have 4 doses, each dose reaches the steady state concentration.

The **10mg** dose : sub-therapeutic, not useful.

The **20mg** dose: (the dose is doubled) a bit therapeutic , but as you can notice the trough is below the MEC, so it's not good

The **30mg** dose: trough, peak and average are in therapeutic range, steady state is reached after 4 half-lives, it's a good dose.

The **40mg** dose: above MTC, so it's toxic.

Notice that all the doses entered the steady state at the same time regardless of the amount of the dose.

If you find the 30mg dose is high you can give any amount of dose between 20-30 and the same effect will result.

*Now let's look at the zero order kinetics (on the **right**) :

-1st dose : steady state, but sub-therapeutic.

-2nd dose : (the dose isn't doubled) it's not going to reach a steady state, because the rate of administration here is faster than the rate of elimination. And in certain stages it becomes toxic.

-3rd dose : toxic, and the 4th dose is the worst, and both don't represent a steady state.

Note: you cannot increase the dose to reach the desired concentration, instead, you have to give it in small increments, or the concentration will increase out of proportion to the amount increased.

Why? When we doubled the amount in both situations, we noticed from the graph that the increase in concentration is different because in the second graph there is saturation of elimination (limited capacity) which means accumulation of the drug which means there is no steady state.

-Now, suppose that a drug has a very long half-life, (example : a drug used to treat cardiac arrhythmias has a half-life of 50 days long, so it will reach its steady state after 200 days!, and because it's urgent and we can't wait that long, we give the patient a **loading dose**)

-Loading dose (LD): a single dose, given to reach therapeutic concentration,it remains in the blood for a certain time and it depends on the *volume of distribution* of the drug.

-And then what? I give more subsequent doses to compensate for the amount of drug lost (to keep the rate of administration equal to the rate of elimination), and that's called **a maintenance dose (MD)**, and it depends on the *clearance* of the drug.

Maintenance doses maintain the steady state of the drug in the body. For example : 8mg/6h this is maintenance dose.

$$LD = VD \cdot \text{Concentration of the desired SS}$$

$$MD = CL \cdot \text{Concentration of the desired SS}$$

-And that's how you treat patients: you give a LD, then MDs

-If the half life is short you don't need LD, just give MDs directly.

Q: Can we control the rate of elimination?

A: Yes, but it's very difficult and not advisable method due to giving extra drugs that effect elimination and it becomes more complicated and effects the natural body processes.

Q: How to know if this half-life needs a LD or not?

A: Depends on the condition of the patient, if he was critically ill, we give a LD, if he has high BP for example, we don't give him.

Q: What if the LD was high compared to the MD? We divide the dose to avoid high concentration and thus toxicity. For example: Assume theMD is 200mg/12h and the LD turned out to be 2g so definitely 2g will cause toxicity so we divide it 250mg/2h and we avoid the high concentration by giving multiple frequent doses.

*the question at the final slide is for you to solve.

Note about the last question where the time needed to reach the steady state is required , the doctor clarified that it should be a therapeutic state or target state since we are giving a loading dose and that steady state should be only due to repeated administration. (The same answer in either case)

-The drug has a long half-life so it needs a LD, C: 1mg/L

-We assume 1st order elimination. And we solve the question ☺

Routes of drug administration

-Enteral route: the route in which the drug gets to the GI tract. (the most common is: oral administration).
-Parenteral route: not oral (likely : all types of injections : IV, intramuscular, subcutaneous..) or could be:
-**Topical** application : if someone had a lesion (in the skin or mucus membrane for example), we give him certain creams, or apply certain drugs..
-Inhalation : if the patient has bronchial asthma, we give him an inhaler (the best way).

-Oral administration (PO) : when the patient swallows the drug/dosage form, not chew, and not under the tongue .
The drug will go through the stomach to the intestine.

* Most absorption will occur in the duodenum, why?
Even if the duodenum is the shortest part but nevertheless it has the largest surface area because it has:
1) It has folds in the mucosa itself.
2) Villi to permit more surface area, and projecting microvilli from it to increase the area even more.
But the absorption can occur in the stomach, duodenum, ileum or the upper part of the gut.
Most of the drug will be absorbed from half an hour to two hrs.

-Oral route is the safest, most convenient (example: it means that oral drugs are more acceptable to people than injections and whatsoever)

*Disadvantages : concentration of the drug when administered orally will be affected by many factors:
-First pass effect.
-Incomplete dissolution and disintegration.
-Microbial flora or gastric acid.
-Alteration of the motility of the GI tract.
-Certain types of food.

Note: sublingual (SL) pills(pills under the tongue) don't count as oral administration, they have faster absorption like IV(because under the tongue there is plenty of blood vessels and fluids), no first pass effect, works best with cardiac arrest patients, we use them for fast action outside the hospital because in one minute the pain will be gone.
Chewing also isn't oral like Aspirin (325g) when it is given to myocardial infarction patients to treat thrombosis.

-Rectal administration (PR): rectum is not designed to absorb, it functions as a reservoir of feces has a small surface area , irregular,

erratic , unpredictable..
Note: if there was a rectal disease, then the drug is said to be topical application for a disease in the rectum.

Parenteral routes :-

Intravenous (IV), intramuscular, and subcutaneous.

-Intravenous: we have two types : **1- bolus(from ball)** : a dose of medication is administered into the circulation rapidly, in a short period. It aims to raise the concentration of the drug in the blood to an effective level.

2- Infusion : using a bag/bottle of fluids, we put the drug in it, inject it, and allow it to pass consistently and slowly into the blood (time duration varies according to the condition, it can be 15minutes-12hrs), works best in emergencies. **Why?** It doesn't have a steady state nor a half life so you don't have to wait to give it. (fast action)

-It has to be always a watery solution not turbid nor oily.

***Disadvantage**: If you made a mistake and the drug finished ,you can do nothing either you cause adverse affects or kill your patients. While in oral administration, You can simply use a **nasogastric tube** to get the drug out, or a **vomiting agent**, as well as **activated charcoal**.

Q: Can IV route cause overload on our body?
A.normally IV route doesn't cause overload on our body, except in heart failure patients because they already have a fluid overload in their bodies.

-Intramuscular : we have 3 main areas : deltoid, vastus lateralis, and gluteus maximus muscles.
-Gladius maximus has the least blood flow so you need a well absorbed medicine.

Note : muscles can accommodate(it means that they can bear large volumes), sometimes patients may even die from blood loss into muscle fibers and you won't even notice it!

*Advantage : you can use aqueous, oily, watery fluids in intramuscular route (while you can't in IV) because it enters slowly from the depot

-Subcutaneous : it's under the skin, however, it bears less volume than muscles.

-In both intramuscular and subcutaneous the drug shouldn't be irritable.

-the rest of the slides are self study as the doctor said.

The end!

"it has been said that something as small as the flutter of a butterfly's wing can ultimately cause a typhoon halfway around the world".

*shout outs to the one and only Lojain Rahahleh!