PHARMACOLOGY

◉ Sheets ○ Slides

Number: 4

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Subject: Half-life and Steady State

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- Activity of cytochrome p450 oxidase differs in different populations.
- so dosing people in japan must be different than dosing people in Jordan for example .in Jordan , we don't really take care of this , but in America and developed countries they take care of this because they want to personalize medicine

- That's because cytochromes are proteins coming from genes and genes are different among different people (single nucleotide polymorphism "SNPs").

example : among Jordanian people there is 3% inactive or mutated CYP2D6 , so if you are one of those 3% and you are taking a drug that must be metabolized by CYP2D6 the concentration of the drug will raise in your blood until it causes toxicity .
That's why you notice different side effects on people taking the same medicine , simply it's because drug metabolism is a variable process so will affect the ability to eliminate drug and the concentration of drug will increase causing side effect.

Also , there is 13% among Jordanians have over active CYP2D6 , that means that the enzyme is going to metabolize the drug faster making the clearance process faster and that means we have lost the drug useful effect , and that's why some patients don't respond toward some drugs .

Inhibition and induction:

- Inhibition

- warfarin is an anticoagulant drug if warfarin concentration goes up it will cause bleeding to the patient, warfarin has a very narrow therapeutic window.

-to describe the warfarin to the patient , we have to stay in the hospital for a week to find the best dose , but generally the dose is 3 or 5 mg or maybe reach 7.5mg

- if a patient taking warfarin(anti-coagulant) took omeprazole (which is used to treat high acidity in stomach) , omeprazole inhibits three CYP isoforms that are responsible for warfarin metabolism , so the patient who is mixing warfarin and omeprazole will suffer from bleeding due to the high amounts of warfarin in blood because it's not metabolized anymore.

- induction

- HIV drug

in treatment HIV the drug dose must stay above the sub therapeutic range or the virus will develop resistance and cause death to the patient.

- if a patient taking HIV drug took rifampin (which is used to treat tuberculosis) , rifampin will induce the metabolism of HIV protease inhibitors , and that will push the dug below the sub therapeutic range , if it still sub therapeutic for 1-2 days the virus will develop resistance to the drug and the patient will die.

- Drug metabolizing enzymes vary with age.

- Young children (1-6 months) don't have Cytochrome p450 system(or little amount) and they will develop

those enzymes with time (within one year they have complete cytochrome p450 activity) , that's why some drugs can't be given to those children.

- For example, clearance of midazolam by CYP 3A4 and 3A5 goes from 1 ml/min/kg to 9 ml/min/kg over first few months of life, that's mean the activity of cytochrome p450 increases so the clearance increase (9 times than first 6 month)
- not all drugs follow this concept there is a drug called Carbamazepine and it has higher clearance in children.

Drug elimination

-it is the process in which the drugs are transferred from the internal to the external environment
- Most of the drug is going to be eliminated through the kidney.
- Young children don't have a mature kidney, and elderly people have low function kidneys, and that's another reason why some drugs can't be given to children.
- Why do we have to reduce the drug dose for elderly people (geriatrics)?
Because their kidneys are at low function level. (They have kidney function limitation)

- Other routes for drug elimination include the bile, intestine, lung, or milk in nursing mother, drugs eliminated by these ways must be very lipophilic.
- 95% of the drug is going to be eliminated by urine.

- To test the kidney function we do something called creatinine clearance test: we inject the patient with creatinine and measure how much is the creatinine clearance.

Age	Scr	CrCl
30	1.1	65
50	1.1	53
70	1.1	41
90	1.1	30

- Creatinine clearance decrease with age meaning that the kidney is not functioning well (the activity of it decrease), so you may have to reduce the dose for elderly people especially when they are given narrow therapeutic range drugs.

In elimination process , drug reach to nephron and in the nephron drug excreted to urine , and there must be a transportation process (passive or active) sometimes if you are taking two drugs they may compete on the site of elimination causing fast excreting of one drug and reduce the excreting of other drug so it will accumulate in the body .

Ex: diuretics inhibit excretion of uric acid cause gout.

Note: patients are different in absorption, distribution, metabolism, and elimination and the obvious determinant of them is the age.

- **Half-life of elimination**: Time for plasma conc. to decrease by half.

It is a value we can use it to understand the real ability of the drug to be eliminated

why do I have to know the half-life of my drug?

In order to know the:

1-time to reach steady state concentration.

2-time for plasma concentration to fall after dosing is stopped.

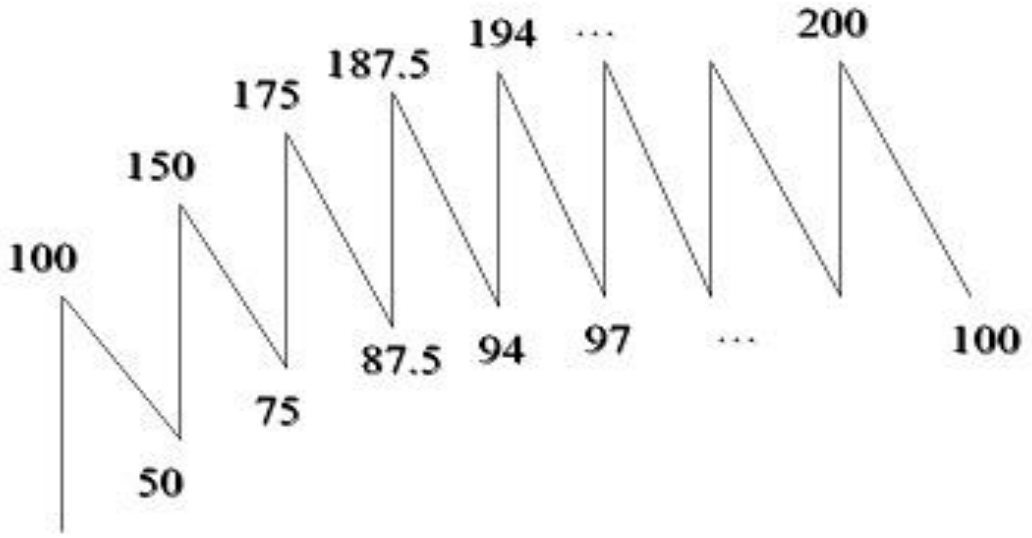
Note: we have to keep the drug within a certain range and this certain range must be active range (therapeutic window)

-On continuous steady administration of a drug, plasma concentration will rise fast at first then more slowly and reach a plateau, where:

Rate of administration = rate of elimination

I.e. steady state is reached.

- Accumulation of drug to reach steady state:



- I dose the patient with 100 then I wait for the first half life, the drug concentration will reach 50 the I give another dose the concentration will raise to 150 and so on until I reach a state where the concentration after dosing is 200 after a half-life it will be 100 then I dose with 100 getting back to 200 and so on, so at the end the concentration will change only from 200 to 100 then I give him 100 going back to 200 and that is the steady state.

- What should I do if I'm dealing with a drug with a short? Half-life (two hours) should I give him 12 dose to reach the steady state?

The answer is no.

There is two solutions depending on the therapeutic

window of my drug.
If the drug has a wide therapeutic window simply I give him a higher dose.
If the drug has a narrow therapeutic window it must be given by injection and dropping.

** You need 4-5 half-lives to reach the steady state for 99% of drugs (there are an exception but we don't care about it).
** You need 4-5 half-lives to have the drug eliminated from the body.

Example: If a patient taking warfarin has to do surgery we have to stop it according to the half-life >> 12 hour is the half-life and we need 5 half-lives so 12*5 equals 60 hours.

Note on reaching the steady state: when you give high initial dose the fluctuation will be wide accordingly so you might get to the toxic range.