SHEET NO. 8

PHARMACOLOGY

DOCTOR 2019 | MEDICINE | JU

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بسم الله الرحمن الرحيم

" All the questions written in purple are of our colleagues' during the lecture "

Review :

1) The target of metabolism is to change the drug towards a more water-soluble state (more hydrophilic state) so it can be excreted and eliminated either by urine or feces .
2) The system consists of two phases (1+2) , in which the first one is catalyzed by CYP450 isoenzymes.
3) (Important) : Those isoenzymes (CYP) can be either **induced** or **inhibited** by other drugs through drug-drug interactions , which results in a **decrease** **or** **increase** (respectively) in drug concentration within blood .
4) (Important) Those isoenzymes are built from proteins that are transcribed from genes which can be polymorphic . This polymorphism is the reason behind variations among populations , and is the base of Pharmacogenetics (personalized medicine) .
5) Usually drugs' clearance in adults is faster than children , like in midazolam's clearance as well as in other drugs . **However** carbamazepine is an exception ; it is cleared faster in children because they have a higher content of CYP(3A4) , so they are given a larger dose of it .

Last time we talked about 3 level of Pharmacokinetics :

1.absorbtion
2.distriburion
3.metabolism(biotransformation)
👇.4

4.Elimination

1) It is a process in which drugs are transferred from the internal to the external environment.
2) Occurs via a number of routes , the most important being through the kidney (the main route) into the urine.
3) Other routes include the bile (by liver itself) , intestine,lung , or milk in nursing mother.
4) Drugs eliminated through these routes tend to be lipid soluble and unionized**.**

Explanation of point 3 :

1.bile = after the drug enters the body and do the biological effect, and goes to be metabolized in the liver by conjugation (the addition of glucuronic acid , sulfuric acid or glucose which makes the drug polar but big >>> so it is eliminated through the bile)
2.Through the intestine means (befor it even enters the body or reaches the targeted cells).
3.lung , by exhaling the gases as in anesthesia , in which the drug enters and exits through our lungs
4.milk : Which happens with nursing mothers , when part of the drug is lipophilic it is excreted with breast milk, and might be transferred to the fetus.
Ex :Mothers who are addicted to taking quinidine (quinidine can be converted to morphine in certain reactions) it is then transmitted through milk to babies whilst breastfeeding , which might lead to respiratory depression then infant death .

Creatinine Clearance vs. Age :

"We are not required to calculated it "

Creatinine is a substance in our body used for measurement of kidney function.

💪if the kidney works very well, it clears creatinine rapidly .

😔But due to kidneys' atrophy, wilt or acute renal failure, the clearance of creatinine will be reduced.

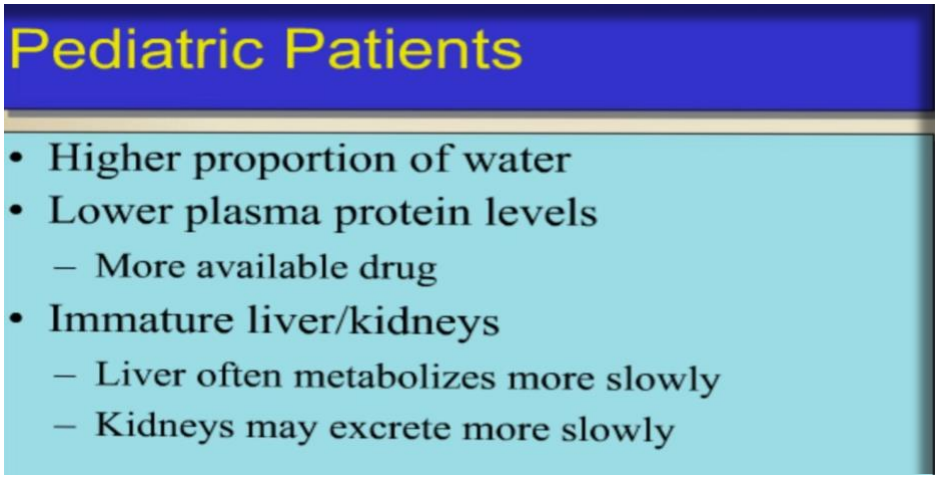
Age	Scr	CrCl
30	1.1	65
50	1.1	53
70	1.1	41
90	1.1	30

** It's really important to deal with patients according to their age , since the clearance if creatinine (which reflects the clearance of drugs) is reduced with age .
This reflects the doses they are given , and here drugs with wide therapeutic window don't really matter , it is those drugs with narrow therapeutic window

and margin of safety that makes proper dosing critical for the safety of older patients .

Why do pediatric patients have higher clearance value ?

Look below :



Pedautric patients have lower plasma protien levels:

Their Liver is less developed and have a lower ability to synthesize plasma proteins , so the drug will be more available (it won't bind to albumin as much for ex.) .

Remember : The free drug is active while the drug bound with albumin is inactive and can do no biological effect .

Q: Does this mean that we always have to give pediatrics lower doses ?

Generally speaking yes , but there are exceptions to the rule including cyclosporine . And as they grow , the dose is increased .

Keep in mind that some drugs are prohibited for children under 6 months , 12 months , 5 years and so on .

It depends on the drug , the way it is taken, the metabolism, the way of elimination, the maturity of one's liver and capability to produce needed enzymes .

Half-life of elimination

It is the time needed for drugs' plasma concentration to decrease by half. Not the original given dose but the one that reaches the bloods plasma .

EX : If 100 mg of drug (A) is given, the bioavailability is 70 mg, then the half-life is the time needed for the concentration to be approximately 35 mg.
E. G: When a patient is taking aspirin (an anticoagulant), and needs to have an open-heart surgery for example , it is necessary to eliminate the aspirin to prevent the occurrence of bleeding , the question is when the patient should stop taking Aspirin pills ?

Now in most drugs like drug x , the drug needs to be stopped 24 hours before the operation (this time depends on the drug's half- life of elimination) , and most drugs need 4-5 half-lives to pass .
Aspirin is an exception : here we count the half-lives needed for the drug's plasma concentration to be reduced , because it binds to cyclooxygenase irreversibly, instead we count the time for the platelets to refunction normally (to coagulate when needed) , and depending on their half life doctors have estimated to need 4-6 days till they function normally again .

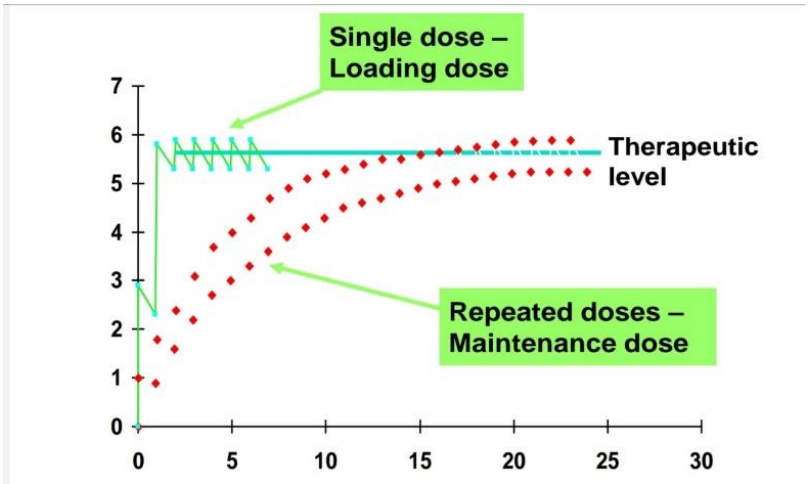
Steady State concentration :

This is used when a certain drug dose is necessary for the operation .

Steady-state concentration is the time during which the concentration of the **drug** in the body stays consistent.

Rate of administration = rate of elimination

For most **drugs**, the time needed to reach the **steady state** is four to five half-lives if the **drug** is given at regular intervals—no matter what the number of doses is , the dose size, or the dosing interval .



When does the drug work?
When the therapeutic window is reached، Which means the concentration that creates the desired effect.
- Anything below that will be considered a lac concentration that gives a slight effect rather than the desired one .

The therapeutic level (shown in green), must be reached , then the drug's concentration should remain constant after that . This requires the steady administration of a drug in which the plasma concentration will rise fast at first then slows down then reaches plateau, where:
steady state is reached.

stready state: When the concentration of the drug entering the blood equals the concentration of the drug leaving the blood, this is mean the steady-state.
The procedure :

1) Drug A is given with a dose of 200 mg , only 100mg reaches the systematic circulation (the 100 mg is what we care about only) .
2) After the first half-life (assuming it to be 4 hours) , the concentration becomes 50 mg . So another 200 mg is given (remember that only 100mg of them reach the plasma) , now the total con. Is 150mg.
3) The second half-life passes by and the con. Is now 75 mg , another 200mg is given (only 100 reaches) the total con. Is 175mg.
4) The third half-life passes by and the con. Is now 87.5 mg , another 200mg is given (only 100 reaches) the total con. Is 187.5mg.
5) The 4^{th} half-life passes by and the con. Is now 93.75 mg , another 200mg is given (only 100 reaches) the total con. Is 193.75 mg.
6) The 5^{th} half-life passes by and the con. Is now 96.875 mg , another 200mg is given (only 100 reaches) the total con. Is 196.875 mg.

Now , notice that from now on , the drug's concentration will be almost 100 each time another dose is given .
And this is what we are looking for to have a safe surgery ☺

**** And most drugs need 4-5 half-lives to reach the steady state .**

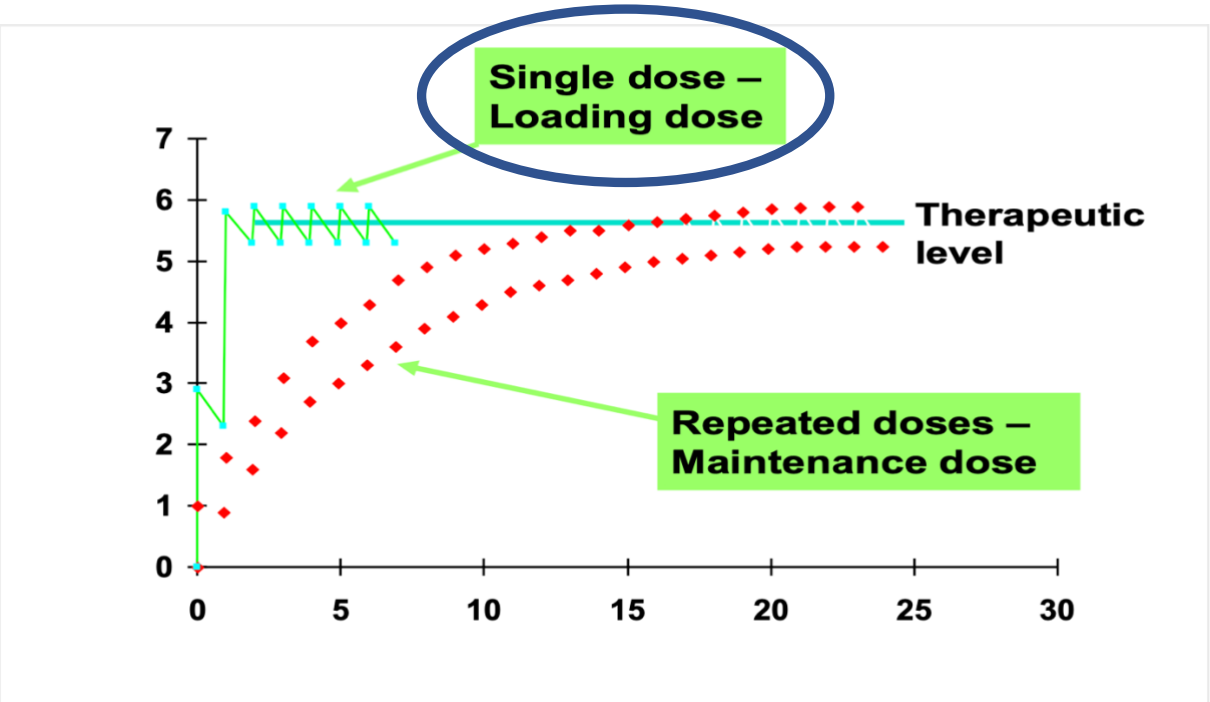
Q: Do all drugs follow this rule ??

No , There are some drug that follow zero order elimination, we don't apply the previous equation, but we give the patient a drug , then levels it's concentration in different mechanisms until we now the proper dose
It's a different way to reach the steady state which is not dependent on the drug's half-life .

Q : Is it necessary to reach the steady state in order to see the therapeutic effect ?

No , the therapeutic effect can be seen before that state but it won't remain constant on the level we need (the max level) because of elimination , so we need to build up the concentration to increase the effect and to have it constant . (based on the dose-response curve).

Loading Dose :



The single loading dose method decreases the time needed for the drug to work and reach the steady state , which is done by increasing the drug concentration within the blood quickly .

** We **try** to use the loading dose with drugs that have a wide therapeutic window , to avoid toxicity .

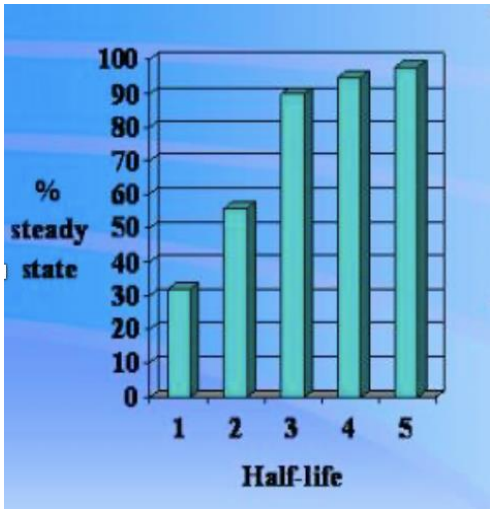
Usage : When there is an urgent need to reach the steady state but no time to apply the repeated does method , this method is used .

Example 1 : A patient came with an urgent need for an angioplasty , in which an antiplatelet drug (clopidogrel) should be given in a steady state manner . So, Instead of the normal dose of (clopidogrel) which is 75mg daily , the patient is given 300 mg orally (4 doses at once) , then another (75)mg the next

day (to compensate for the eliminated portion) , thus the steady state will be reached quickly .

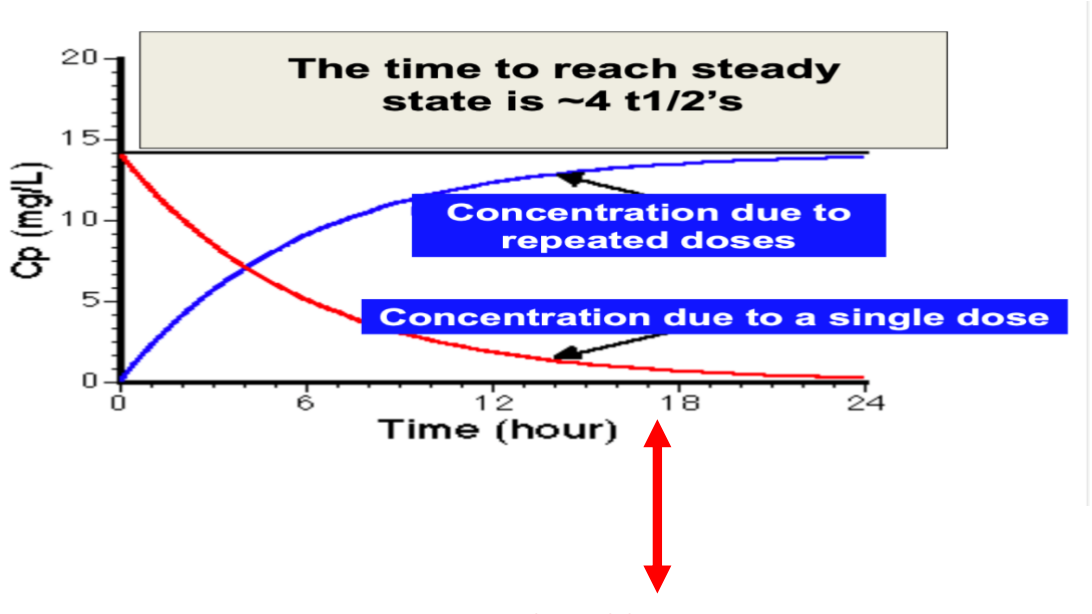
Example 2 : In the ER the patient can be given an injection with a certain loading dose then followed by a drip (continuous administration of the drug as drops) to compensate for any elimination . Thus , (steady state) :
Rate of administration = Rate of elimination

Half-life = time required for serum plasma concentrations to decrease by one-half (50%) .
4-5 half-lives to reach to reach steady state .



(We don't need to calculate the loading dose , but you can look it up if you want)

The time needed to reach a neglectable concentration (IMP)



Neglectable concentration

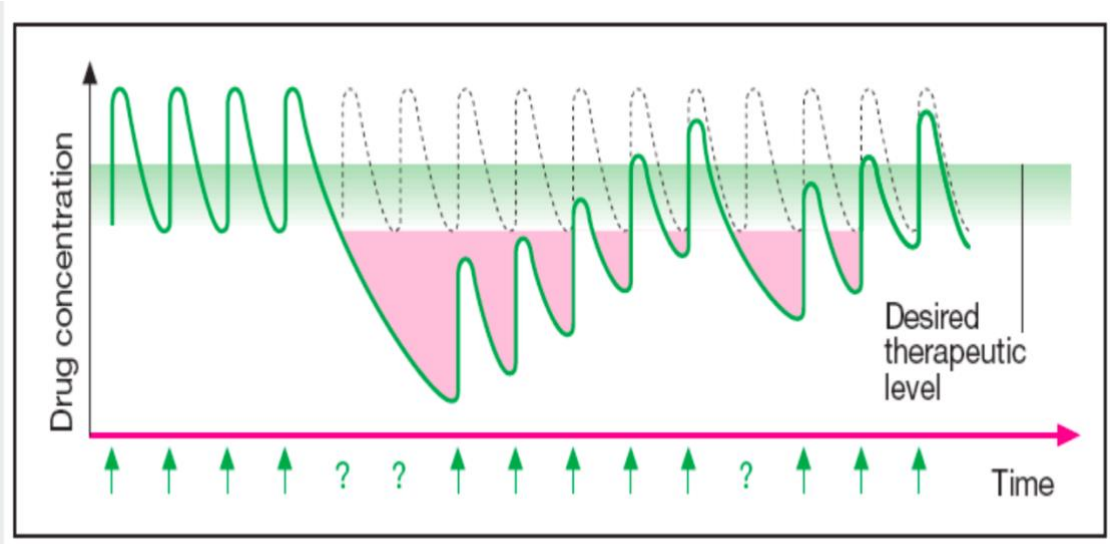
The time needed for the drug's concentration to becomes neglectable (not effective) , which is calculated since the last administration .

Example : Drug A is at **100mg** concentration in blood , after 4 hours (the half life) it becomes **50 mg** , after another 4 hours it becomes **25 mg** , then **12.5mg** , then **6.25mg** , then **3.125mg** (which is a non-effective dose))
➡ So , we needed 5 half-lives to reach a neglectable concentration .

(Remember : Previously , we studied the time needed to reach a steady state , now we are studying the opposite **)**

Usage :
1) To eliminate the drug to prevent drug-drug interaction with another .
2) Before certain surgeries , to make sure that a certain drug has stopped working .
Example : Glucophage (Metformin) is stopped 2 days (4 half-lives) prior to kidney scanning , because it interacts with the dye given before the scan .

Adherence (compliance) toward drugs :



Time course of drug concentration with irregular intake

Compliance : whether the patient sticks with the doctor's instructions on the frequency and dose of administration .
What is the problem with patients' non-compliance ?
A : They won't benefit from the drug's biological effect . How ?

Patient (A) took the drug as instructed for 4 consecutive days , so a steady state was built . Then he missed taking it in the 5th and 6th day , so the drug started to be eliminated . He then re-took the recommended dose for few days then stopped again .
What actually happens is that the drug will not be built up eventually , it won't reach the needed steady state nor the desired therapeutic level , so there will be little to no benefit .
The patient is non-compliant .

Example : Skipping a dose (ex . morning dose) of an antibiotic will lead to bacterial proliferation , even if the patient took the night dose .
Because both of them are needed to have the effect as explained above .

Drug-drug interaction :

1) When two drugs are taken together, there is a possibility that the drugs will interact with each other to cause unanticipated effect. Usually increase or decrease in the desired therapeutic effect.
2) Drug-drug interaction can occur in the following sites :

a. at the side of absorption, tetracycline is not absorbed from the GI tract if calcium product present in the stomach.
b. during biotransformation (CYP 450).
c. At the site of action, dug antagonism.

Drug-drug interaction

3) During excretion, digoxin and quinidine are both excreted from the same sites in the kidney. The quinidine will be excreted first because it is more competitive for these sites, resulting in increased serum levels of digoxin (has a narrow therapeutic window -toxicity-).
4) During distribution, aspirin competes with methotrexate for protein binding sites, and because aspirine is more competitive for the sites, resulting in increased release of methotrexate and so increase toxicity to tissues.

REMEMBER
No drug produces a single effect!!!

Adverse effects :

Adverse effects are undesired effects that may be unpleasant or even dangerous they can occur for many reasons:

1. The drug may have other effects on the body besides the therapeutic effect.

Explanation : Why does the drug have adverse effects ?

1) Physiological effect : **Receptors are tissue specific and they function differently according to the tissue**

Receptors for a certain drug may be distributed in many areas within the body (e.g. heart , brain , liver , kidney, etc.) , and each receptor will give a response in a way specific to the tissue it's present in . This is called "Tissue **specific receptor activity** "

2) Biochemistry effect: **Receptors homology and relative selectivity**

The targeted receptor might have another homologous receptor e.g. the targeted **β1** receptor has other homologies which are **β2 , β3 ,α1 ,α2** receptors → 90% of the drug will bind to **β1** the other 10% will bind **β2 , β3 ,α1 ,α2**

There is nothing called absolute selectivity (no drug can bind to only one receptor)

In medicine there is only **Relative Selectivity** → The drug may have the highest affinity to the targeted receptors and give the wanted effect, but unfortunately the 10% (for example) bound to other homologous receptors might cause serious adverse effects .

Although we dose to all patients in a similar way (in kg according to BMI) , each patient will experience different side effects e.g. we dose Ciclosporin and a percentage of patients will have gingival hyperplasia some will have diabetes mellitus and hypertension.

2. The patient is sensitive to the drug.

The patient may be sensitive to sulfur, penicillin diclofenac. each person has his/her own way to recognize a specific drug in some patients they

That's why some people die from COVID-19 and others don't experience as much pain their immune system recognize the virus in an exaggerated manner and this cause cytokine flare which will attack the lungs and eventually lead to death (like the concept of autoimmune diseases)

3. The patient is taking too much or too little of the drug.

Why is too little of a drug harmful?

When you take the prescribed amount of drug you kill both the good and harmful bacteria. however too little of a drug will Kill Microflora (which is not resistant in its nature) and keep the harmful bacteria which will become dominant this will lead to **super infection**

Note: some microbiome can't develop resistance in its nature

E.g, microbiome in skin Strep. cocci and staph. aureus → mrsa infection is caused by a type of staph bacteria that's become resistant to many of the antibiotics used to treat ordinary staph infections

E.g. Microbiome in GI lactobacillus

Clostridium difficile is resistant in its nature an develop more with time

• the nurse, as the most frequently administers medications, must be constantly alert for sign of drug reactions of various types.

adverse effect

• with every drug use, unwanted effects must be taken into account beforeprescribing a drug, the physician should therefore assess the **Risk: benefit ratio**. The benefit should outweigh the risk

• knowledge of principal and adverse effects is a prerequisite.

Are drug adverse effects dynamic or static?

It is dynamic according to patient's status, and risk to benefit ratio is what determine whether or not prescribe a certain drug.

For example

- Cyclosporin for normal patients the benefits outweigh risk

But for patients with liver failure the risk will outweigh the benefit

- For young kids risk of toxicity is always more than benefit that's why drugs are contradicted

Same applies to old patients

- Profin and diclofenac may not have high risk on old patient but is extremely harmful for those who have kidney failure.

Before you prescribe a drug you should be certain that drug's benefits are more than it's toxicity .

Follow the movement , Speak up !!!