Pharmacology

Sheets Slides

Number: 3

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Subject: Pharmacokinetics

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- In previous lectures, we talked about transporters in the body, the most important transporter in the body is P- glycoprotein (MDR-1).

- P-glycoprotein is a transmembrane transport protein, responsible for transporting various molecules, including drugs, across cellular membranes. This protein is the site of activation or inactivation, so many drugs may inhibit or induce this protein thus affecting the absorption of the drugs.

Absorption:

Factors influencing absorption:

1. Blood flow to the absorption site.
2. Total surface area available for absorption.
3. Contact time at the absorption surface.

- The 1st and 2nd factors make the duodenum the main site of absorption.

- The 3rd factor is a very important determinant of the kinetics of the drug, that means for the level of drug in the blood,

Case 1 :

if a patient has diarrhea, the drug will not have enough contact time for absorption, so the drug will go to the stomach then to the duodenum then to the jejunum then will be secreted quickly without enough absorption time.

Case 2:

Geriatrics (adults >65 years old) have problems such as constipation. Those patients will have more time for the drug to be absorbed because it will stay longer.

- You have to take into consideration that when you dose your patient, the drug level absorbed by the blood will be changed according to physiological or pathological conditions of formation.
  - In cases of diarrhea:
    when you give a tablet, this does not mean the drug is effective because it may not absorbed, or may not reach the therapeutic level, or the concentration to produce therapeutic effect.

  - Therapeutic range: the range between the minimal effective concentration (MEC) and the minimal toxic concentration(MTC).
  - Any concentration below this level is considered subtherapeutic.
  - Any concentration above this level is considered toxic.

Bioavailability (Dynamic state): is the rate and extent to which an administered drug reaches the systemic circulation. For example, if 100 mg of a drug is administered orally and 70 mg is absorbed unchanged, the bioavailability is 0.7 or 70%. Determining bioavailability is important for calculating drug dosages for non-intravenous routes of administration.

- We said :

a- “non-intravenous” because in IV administered drugs , 100% of the drug reach the systemic circulation (F=1). F is bioavailability.

b- “absorbed unchanged” because some of the absorbed drug may be

changed during hepatic metabolism.
→ Bioavailability deals with the amount of the drug that reaches the systemic circulation in the active form (unchanged form).

- Bioavailability is determined by absorption itself, and absorption is controlled by time of contact between the drug and the site of absorption and stability of the drug.

Also, it is determined by:

1. Contact time between the drug and the duodenum.
- We said "duodenum because it's the main site of absorption , but the drug can be absorbed at any other site".

2. First pass metabolism level.

Determination of the bioavailability of a drug. AUC = area under curve; IV = intravenous.

-By plotting plasma concentrations of the drug versus time, the area under the curve (AUC) can be measured. The total AUC reflects the extent of absorption of the drug. Bioavailability of a drug given orally is the ratio of the AUC following oral administration to the AUC following IV administration (Assuming IV and oral doses are equivalent).

If your patient has liver problems → elimination through hepatic metabolism will be affected → less elimination → increased bioavailability.

constipation → time of contact between the drug and the site of absorption increases → more absorption → higher bioavailability

diarrhea → less time of contact → less absorption → decreased bioavailability.

- Bioavailability is also determined by the lipophilicity of the drug.
lipophilic → able to cross the membranes → more readily absorbed → Higher bioavailability.
lipophobic → isn't able to cross the membranes → less absorption → decreased bioavailability.

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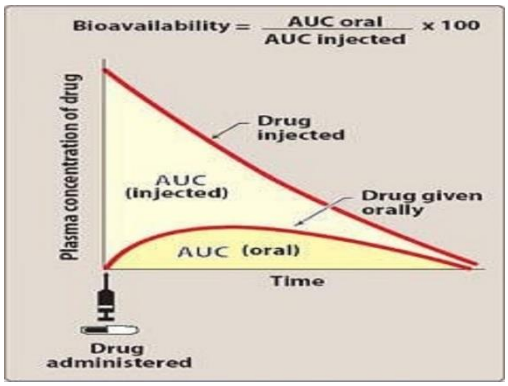

- Bioavailability for children is different from old people.
- If your patient has liver cirrhosis → less metabolism → higher bioavailability.
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- Refer to slide 46: All of these effects mostly in the liver

- Drugs that go into extensive first-pass metabolism show very low bioavailability , so it's better to administer them intravenously.

If you give a patient a suppository, the drug will have reduced first pass effect, because only 50% of the blood carrying the drug will join the portal circulation.

Mostly drug absorption can be affected by other determinants (like food), so some of what you eat can render the absorption of your drug, because absorption is competitive and the drug and food compete on it.

Sometimes, you tell the patient " take the drug with food " , why ?
Because if this drug is taken without food, it will cause irritation effect, for example, ibuprofen.

-Should tablets be taken before, during, or after meals?
There is no simple answer for this question. However, as a general rule you should take medicine on an empty stomach, unless told to take it with food (one hour before eating or 2 hours after).

This is because many medicines can be affected by what you eat and when you eat it. For example, taking a pill at the same time you eat may interfere with the way your stomach and intestines absorb the drug. If you have food in your stomach at the same time as you take a drug, it may delay or decrease the absorption of the drug.
There are many exceptions to this rule. Some drugs, are easier to tolerate with food. It may be preferable to take them with or immediately after a meal to reduce the risk of side effects and if this drug is taken without food, it will cause irritation effect, for example, ibuprofen
.
The amounts of the drug which reach the blood will change.

If the drug is taken at a/an
Empty stomach → this drug has high reaction with food.
Full stomach → this drug is not affected by food, for ex, ibuprofen.

1. Take medicine with water not with juice or milk and take capsule apart.
2. Do not dissolve the drug in water.
3. Do not take vitamins pills at same time with medicine, because vitamins and minerals (like Magnesium,Aluminum, Iron, Calcium) can cause problem with drugs.
4. Do not mix medicine with hot water, because the heat might affect the drug.

Distribution:

Is the branch of pharmacokinetics which describes the reversible transfer of drug from one location to another within the body.
(between the blood , interstitial fluid and cells)

- Duration of drug action in the body increases → distribution in the body increases.
- Water is found in plasma in blood, in interstitial fluid, cells.
- Adult human body contains about 45 liters of water.
- Distribution is determined by: molecular weight and hydrophilicity or hydrophobicity.

- Volume of distribution (Vd):

The apparent volume of distribution, Vd, is defined as the fluid volume that is required to contain the entire drug in the body at the same concentration measured in the plasma. It is calculated by dividing the dose that ultimately gets into the systemic circulation by the plasma concentration at time zero (Cp at time zero). “p” stands plasma.

Vd = Amount of drug in the body/ Cp
Although Vd has no physiologic or physical basis, it can be useful to compare the distribution of a drug with the volumes of the water compartments in the body.

Vd values :
1- (2-5) L → the drug tens to stay in the plasma.
Characteristics of the drug in this case :
a- has very large molecular weight **OR**
b- binds extensively to plasma proteins.
So the drug is effectively trapped within the plasma (vascular) compartment.
- In this case the drug will distribute in a volume that is about 6% of the body weight.
- For example, in 70 kg individual, agents of this type, such as Heparin, will distribute in 4 L of body fluids.

2- 14 L → it tends to be in the extracellular fluid.
characteristics of the drug in this case:
a- has low molecular weight but it is hydrophilic, it can move through the endothelial junctions (can go from the blood to the interstitial fluid) but cannot cross the membrane to enter the cells.

- So, drugs like aminoglycosides, will distribute into a volume equal the sum of the plasma water and the interstitial fluids (14 L in a 70 kg individual)

3- 42 L → it tends to be anywhere in the body (in the plasma , cells and interstitial fluid).
- 42 L means total body water.
characteristics of the drug in this case :
a- has low molecular weight and hydrophobic, here the drug move through the membranes into the cells.
- Here the drug will distribute into a volume of about 60% of the body weight (42 L in a 70 kg individual).

- ”Children are not small men”, said Dr.Malik.
  That means young people are different from old people in the distribution of muscle, fats, and water.

In narrow-therapeutic-range drugs, we take into consideration different physiological conditions or different body compositions, while in wide-therapeutic-range drugs , you can use quarter of the dose.

***Pharmacokinetics Adults >65 years old**:
Decrease in total body water (due to decrease in muscle mass) and increase in total body fat affects volume of distribution
•Water soluble drugs: ex: digoxin
–Serum levels may go up due to decreased volume of distribution.(why does the VD decrease ?
because of the decrease in total body water and increase in total body fat.

•Fat soluble:
–Half life increased with increase in body fat.

***Pediatric Distribution**
Body Composition
- Increased total body water & extracellular fluid.
- Decreased amount of adipose tissue & skeletal muscle.

- Drugs can be:

  1. Water soluble (hydrophilic / lipophobic): stay in plasma and interstitial fluid.
  2. Fat soluble: stay a long time in the body.

* Most of the drugs are carried on the albumin,but not all of them.
* Binding of the drug to albumin is reversible.

* **Drug interaction** is a situation in which a substance (usually another drug) affects the activity of a drug when both are administered together.

- Drug interactions may lead to increased effect or decreased effect.
If the second drug binds albumin with higher affinity , my drug will dissociate and that will result in increased effect. (the concentration of the free form of my drug increases).

- You can think of it in the other way around.

-Typically, interactions between drugs come to mind (drug-drug interaction). However, interactions may also exist between drugs and foods (drug-food interactions).

The bound drug is kept in the blood stream while the free (unbound) component may be metabolized or excreted, making it the active part.

So, if a drug is 95% bound to a binding protein and 5% is free, that means that 5% is active in the system and causing pharmacological effect.

If you give another drug that has a higher affinity to bind albumin, it will expel your drug from the albumin which is dangerous in the narrow therapeutic index drugs.

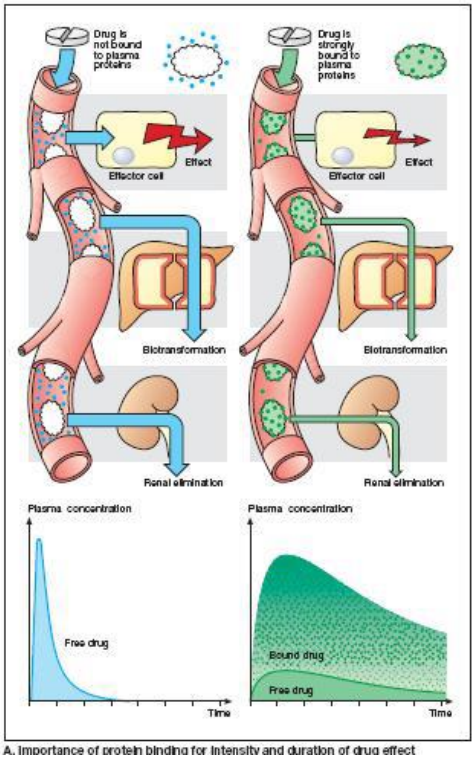
Why is it dangerous in narrow-therapeutic-range drugs not those with wide therapeutic ranges ?

Because expelling my drug from albumin will increase the amount of the free drug , resulting in a higher concentration of the active drug. So, if my drug has a narrow therapeutic range , this increase in concentration may lead to reaching toxic concentrations. In wide therapeutic ranges , this increase in concentration may increase the effect without reaching toxic concentrations.

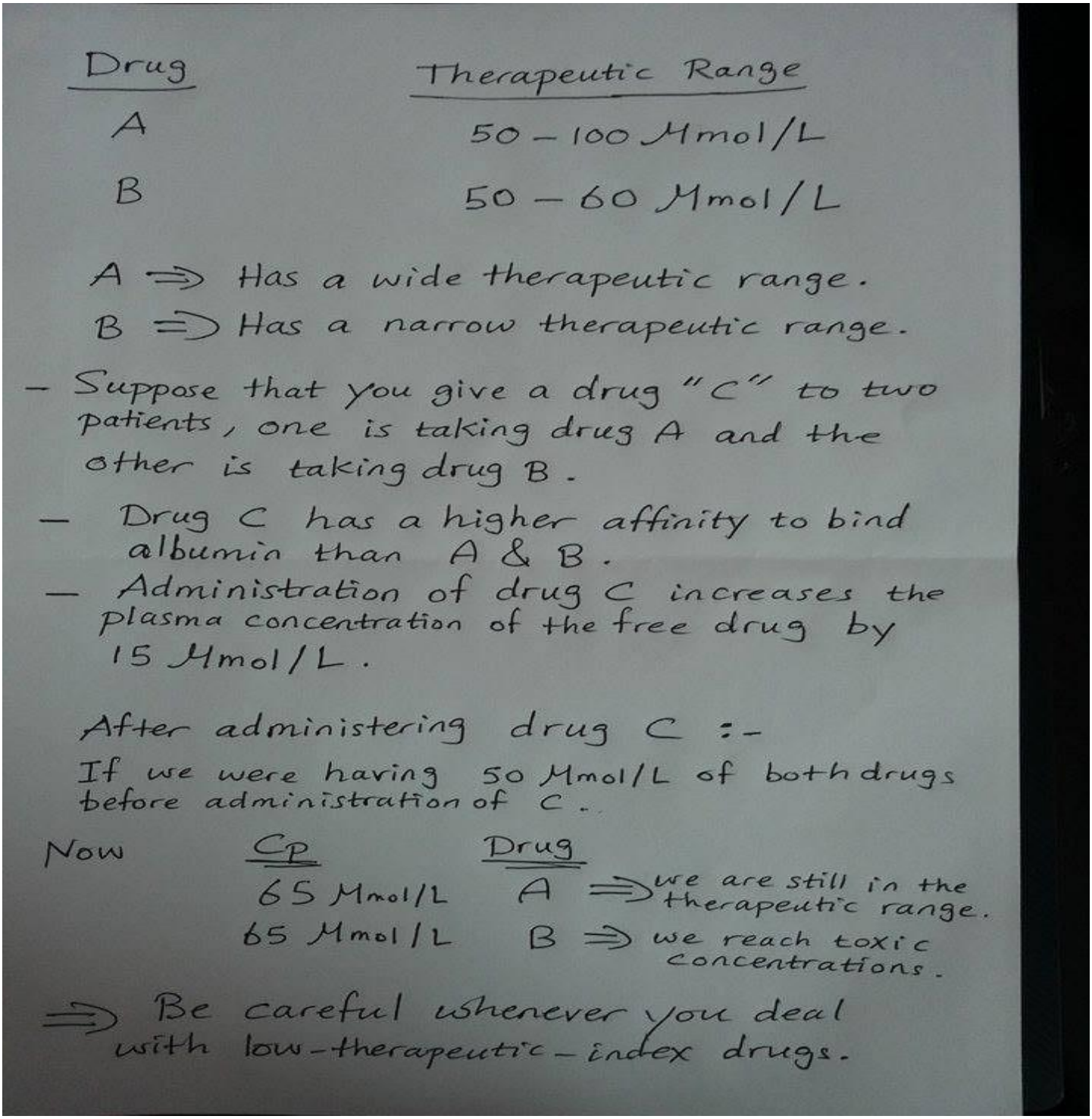
Free (unbound) drugs: active drugs.
bound drugs: inactive drugs.

There is equilibrium in the body between free drugs and bound drugs.

When you give another drug, it will compete on the binding site of albumin. We distribute the drug alone, not other drug.



A. Importance of protein binding for intensity and duration of drug effect



For example, morphine, all of its parts bind to albumin→ highly binding to albumin.

Drugs undergo binding to protein. The efficacy of a drug is affected by the degree to which it binds to proteins in the blood plasma. The less

binding a drug , the more efficiently it can cross cell membranes.

A drug exists in two forms in the blood: bound and unbound to (free).

Depending on the specific affinity of the drug for plasma proteins, a portion of drug may become bound to plasma proteins, while the rest remains unbound. If the binding protein is reversible, then a chemical equilibrium will exist between bound and unbound states, such that: Protein + drug ↔ protein-drug complex

It is the fraction unbound (or free) that displays pharmacological effects. It is also the fraction that may be metabolized and / or excreted. For example, the " bound fraction" of the anticoagulant warfarin is 97%. This means that 97% of all warfarin present in the blood is bound to plasma proteins. The remaining 3% (unbound fraction) are a fraction of what is really active and can be excreted.

Metabolism: (most important process)

It affects elimination.

Most important part of drug – drug interaction.

It causes the different response for the drugs.

When the drug ends its distribution, it exerts its activity on the receptor.

The liver is the major

Such as lungs and kidney can also metabolize drugs.
side of metabolism form for any drugs, but other organs,

Metabolism occurs to get rid of drugs from the body mostly through kidney, excretion of the kidney is mostly water, so I need to increase hydrophilicity through oxidation by Cytochrome P450 system → drugs more hydrophilic → can be excreted with urine.

Cytochrome P450 system is responsible for phase Ⅰ metabolism.

Cytochrome P450 → oxidizes the drug → drug is modified in a way that will make it hydrophilic and makes it easier for the kidney to eliminate the drug.

If phase Ⅰ is not enough (the drug isn't hydrophilic enough to be excreted with urineafter phase Ⅰ reactions) , I have to apply phase Ⅱ metabolism.

In phase Ⅱ metabolism, you need to add a functional group (polar group) to a drug to oxidize out the body through the urine. (this group can be glucuronic acid or sulfuric acid).

Phase II consists of conjugation reaction with endogenous substances, such as, glucuronic acid, sulfuric acid, or an amino acid.

- Since phase I reactions are done using enzymes, these enzymes can be activated or inhibited.

- Inducers and inhibitors can be drugs.

If a drug is metabolized by a certain enzyme, and we give a second drug that's metabolized by the same enzyme , we will have inhibition of metabolism of the first drug.

- Metabolism can be changed (either decreased or increased) according to the changes produced by the second drug.

- 95% of drugs are metabolized by phase I metabolism by cytochrome P450.

Every drug has a specific enzyme which metabolizes it and the drug is not metabolized by other enzymes (selectivity).

- Metabolizing enzymes, for example:

CYP1A2, CYP2D6, CYP2C9, CYP2E1, CYP2C19, and CYP3A4.

Some drugs are metabolized by cytochrome1A2, or

If your drug is metabolized by cytochrome1A2, and you take another drug which is regulated by CYP2C9, cytochrome1A2 won't be affected.

If the enzyme is inhibited by the second drug →drug metabolism decreases → half life increases → level of the drug in the blood increases → toxicity.
- If it's a wide-therapeutic-range drug , it may not lead to toxicity.

In different people and different populations, activity of CYP oxidases differs, that means Chinese is different from Jordanian in cytochrome activities, because of genetics, why do we have variation in drug response? Why not all patients respond to drug? Why is the level of the drug in the blood different? If we give a group of students a drug, we notice 10% of them differ in the response to the drug and in the metabolism.

* Cytochrome P450 system dependant enzymes are important target for drug interaction because they can be induced or inhibited by certain drugs.

* Cytochrome enzymes Inducers like rifampin and carbamazepine are capable of increasing the synthesis of one or more of isoforms. For example, Rifampin significantly decreases the plasma concentration of HIV protease inhibitors.
. → if the patient takes drug X, metabolism of the drug increase → excretion of the drug increase. In this case, if the amount of the drug increased the required quantity → death.

*Cytochrome enzymes inhibitors, omeprazole (دواء الحموضة) inhibits three CYP isoforms that are responsible for warfarine metabolism, leading in an elevation in the warfarin concentration, and so greater inhibition of coagulation, leading in more risk of serious bleeding reaction.

Remember that you have to link what's written here in the sheet to our doctor's slides.
Memorizing what the doctor said during a lecture had never been a source to study from and it will never be. Slides were written while the doctor is sitting in his office or at home , drinking coffee and having a good mood , or are taken literally from the textbook , so they are a better source to rely on. (They are not enough of course , but the sheets are based on them and explaining them) ..
Sheets are they way to understand the slides … please don't memorize everything…

- Google anything you don't understand well …search for an explanation on youtube …
Don't memorize everything by heart …
What you undertand well will remain with you forever

هذا الفصل مش سهل ... وفيه 100 طن معلومات كل يوم ... فاا ادرسوا

ومن يتوكل على الله فهو حسبه "... تأمل هذه الآية بترتاح :D"

Don't memorize the names of drugs ... they are just examples

Sorry for any mistakes.