Modified slides

Pharmacology

Lecture #8

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Ju dentistry.com

همّةُ الأسْنان

Pharmacokinetics (Continued)

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Distribution :

انه ينتقل الدواء من الدم إلى الأماكن المختلفة من الجسم

Through circulation and interstetium

Drug Distribution: reversibly leaving the blood stream —> interstitium (ECF) —> cells

Distribution Variables

The delivery of drug from the systemic circulation to tissues

(1) capillary permeability Next page (red)

(2) blood flow–tissue mass ratio (i.e., perfusion rate),

(3) extent of plasma protein and specific organ binding

(4) regional differences in pH, Next page (blue)

(5) transport mechanisms available أنه إذا بحتاج transporter زي ال levodopa ولا لأ

(6) the permeability characteristics of specific tissue membranes.

Capillary Permeability: depend on two factors

1- structure of capillary ;

Ex: in brain : the capillary is continuous and there is no slit junction , we have tight junction , these are characteristic of BBB , which only allows only certain molecules to enter , so protect the brain

ف إذا الدواء بده يدخل الدماغ ، محتاج active transporter

مثال : levodopa drug

For psychological disorder as Parkinson

ف هاد اله active transporter عشان يفوت ، اسمهم amino acid transporter

بدخل amino acid like tyrosine

لانه التيروسين مهم لتصنيع ال neurotransmitters in the brain

The liver or spleen in the other extreme

Large portions of basement membrane espoused (fenestratiin) discontinuous capillaries

يسمحوا لل large plasma proteins انها تمرّ

هاي النقطة متشابكة مع نقطة ٦

2- structure of the drug (chemically)

Hydrophobic (no net charge , equally distributed charge of electrons) can pass

But hydrophilic can’t

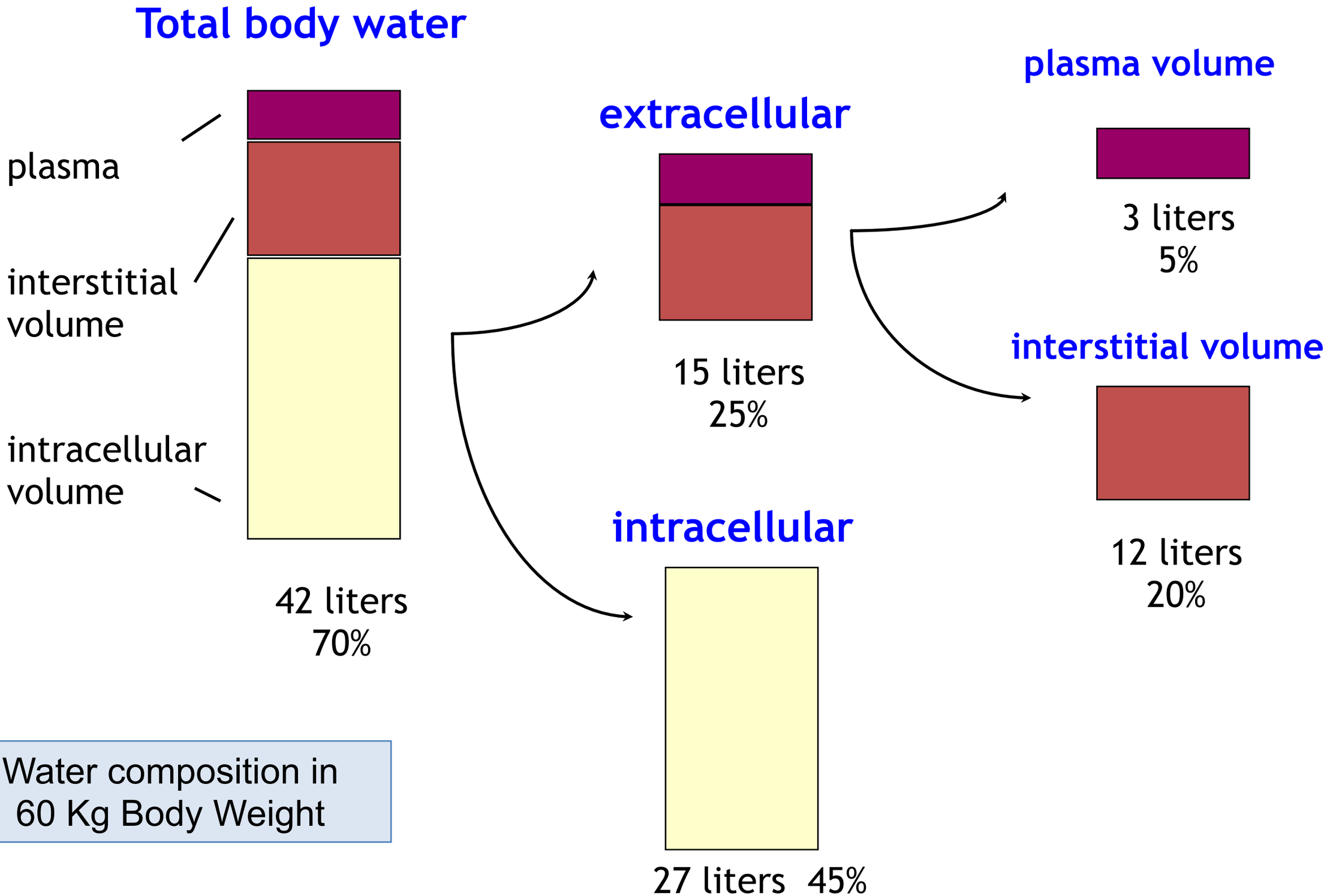
تذكروا لما حكينا بال absorption
انه ازا الدواء weak acid بحبّ البيئة ال acidic
و نفس الاشي بصير هون بال distribution
مثال (مشكلة) : بدي أعطي مخدر اللي هو عادة قاعدي
لمريض مجروح (و الجرح بيئة حمضية) ف هاي هي المشكلة بالاختصار ⬇️

.Let's give an example
.So local anesthetics are actually weak bases
So we said for weak bases the drug will only be absorbed if
.it's in the uncharged form or nonionized form
.So in an acidic environment most of the drug of the weak base will be ionized
So if we have an inflammation or an infection happening in a certain area, let's say we have a skin absess and we
need to perform a procedure on that absess. So before we start with the procedure, we have to anesthetize the
.area with a local anesthetic and we said most local anesthetics are weak bases
So after the injection of this weak base because the environment of the absis is acidic :

most of the local anesthetic will be unfortunately in the ionized form.
Thus we will have limited or less anesthetization of that area as if we compare it to a normal non-pathological area with where the pH is higher than an acidic pH.

لكن !
Another thing now we know that local anesthetics work by inhibiting sodium channels in nerve axons. Now once the local ansthetic enter into the inside of the cell or to the nerve axon it will be ionized there because inside the cell we have a lower pH than outside of the cell. And this ionization can be advantageous in this case because it will trap the local anesthetic inside the cell where it cannot diffuse back to the different tissue and it can perform its action.

Drug distribution and Body water



Water composition in
60 Kg Body Weight

Distribution

The total volume of the fluid compartments of the body into which drugs may be distributed is approximately **42 L** in a 60-kg adult.

These compartments include:

So the drugs will distribute amongst these different compartments depending on the certain characteristics of the drug molecule itself.

- Plasma water
- The interstitial fluid
- The intracellular fluid

1 Plasma:

لانه مو قادر يمر من ال endothelial layer lining the inside of the blood vessels ولا قادر يعبر ال slits (junction)

Drug has very large molecular weight or bind extensively to the plasma proteins. So the drug is effectively trapped with the plasma (vascular) compartment.

In this case the drug will distribute in a volume that is about 6% of the body weight.

Heperin is an anti-coagulant drug that is used for patients who have coagulation problems, like cardiovascular conditions such as myocardial Infarction or deep vein thrombosis. to prevent the reoccurrence of these events.

for example, in 60 kg individual, agents of this type, such as Heparin, will distribute in 3 L of body fluids.

✅ it is convenient (يقلل تخثره) انت رح تفكر انه اشي سيء انه يضل بالبلازما ، بس لأ هاد اللي أنا بدي اياه اصلاً ، في الاخير أنا بدي اياه يشتغل عالدم

Distribution

2. B. Extracellular: has low molecular weight but it is hydrophilic, it can move through the endothelial junctions but cannot cross the membrane to inter the cells.

Slit junction

C. So drugs like aminoglycosides, will distribute into a volume equal the sum of the plasma water + and the interstitial fluids. =ECF 25٪

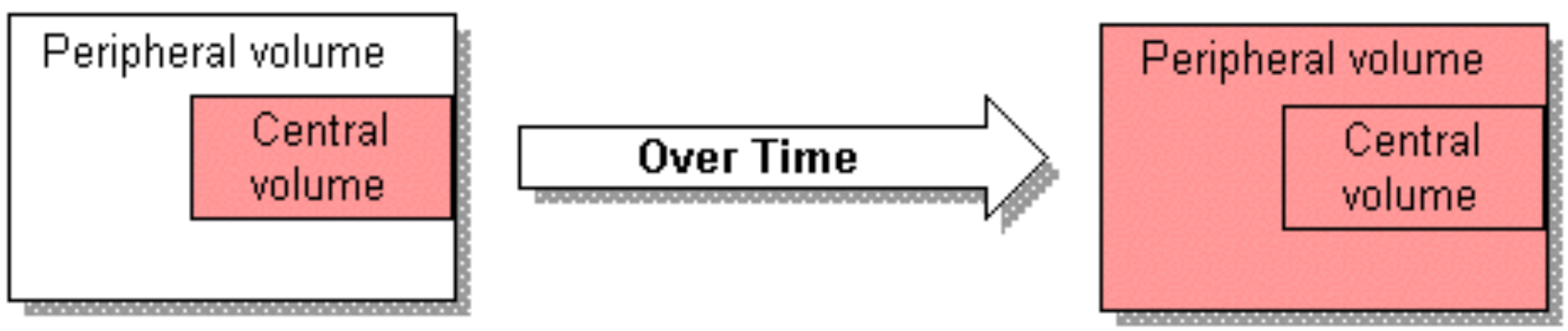
3. C. Total body water: has low molecular weight and hydrophobic, here the drug move through the membranes into the cells. Here the drug will distribute into a volume of about 60% of the body weight.

note: Some drugs, lipid soluble ones, stored in the fatty tissue in an equilibrium with free circulating drug affinity to specific tissue الدواء عنده

موضوع جديد و مهم ، بساعدنا نفهم ال distribution among different tissues
هو رقم افتراضي مو حقيقي (not actual) hypothetical يعني احنا أعطينا هاد الرقم عشان يعطينا فكرة قديش رح يصير توزيع للدواء

Volume of Distribution (Vd)

- **A measure of the tendency of a drug to move out of the blood plasma to some other site.**
- **Or A measure of extend of distribution**



Volume of Distribution

يعني هيك بيظهر للعيان انه الدواء رح يتوزع خلال هاي الvolume و
بنعيد و بنكرر هاد الvolume افتراضي مو فعليًا حقيقي

- 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 (C0).

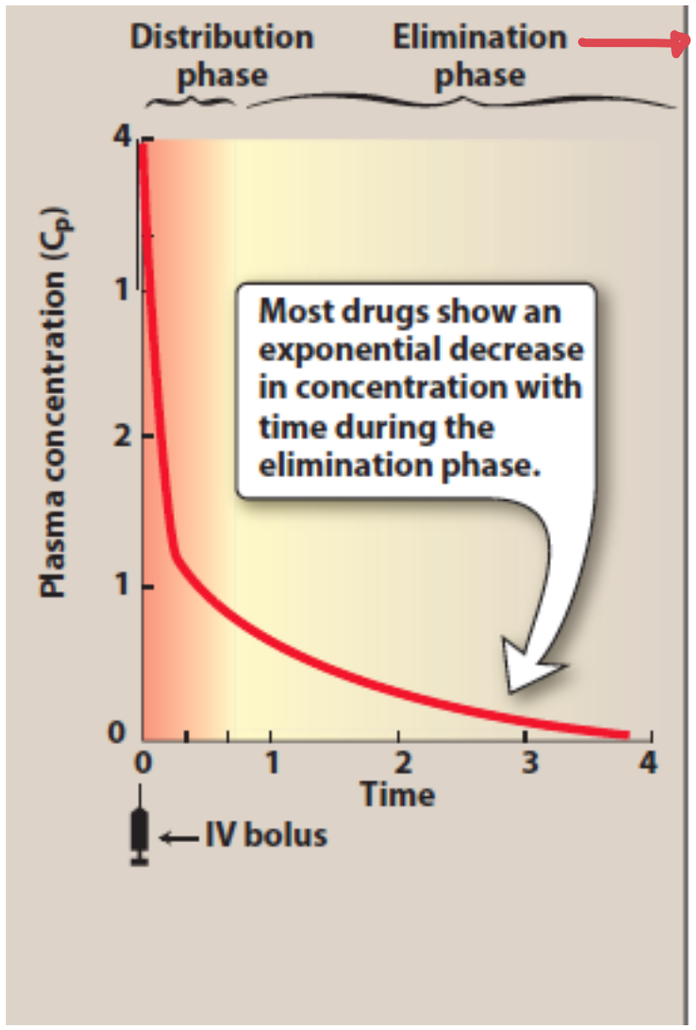
الشرح بالسلايد الجاي
اللي بالعربي : اعادة صياغة
اللي بالإنجليزي كلام الدكتورة الحرفي
الموضوع بسيط جدا بس الكلام طويل

$$V_d = \frac{\text{Amount of drug in the body}}{C_0}$$

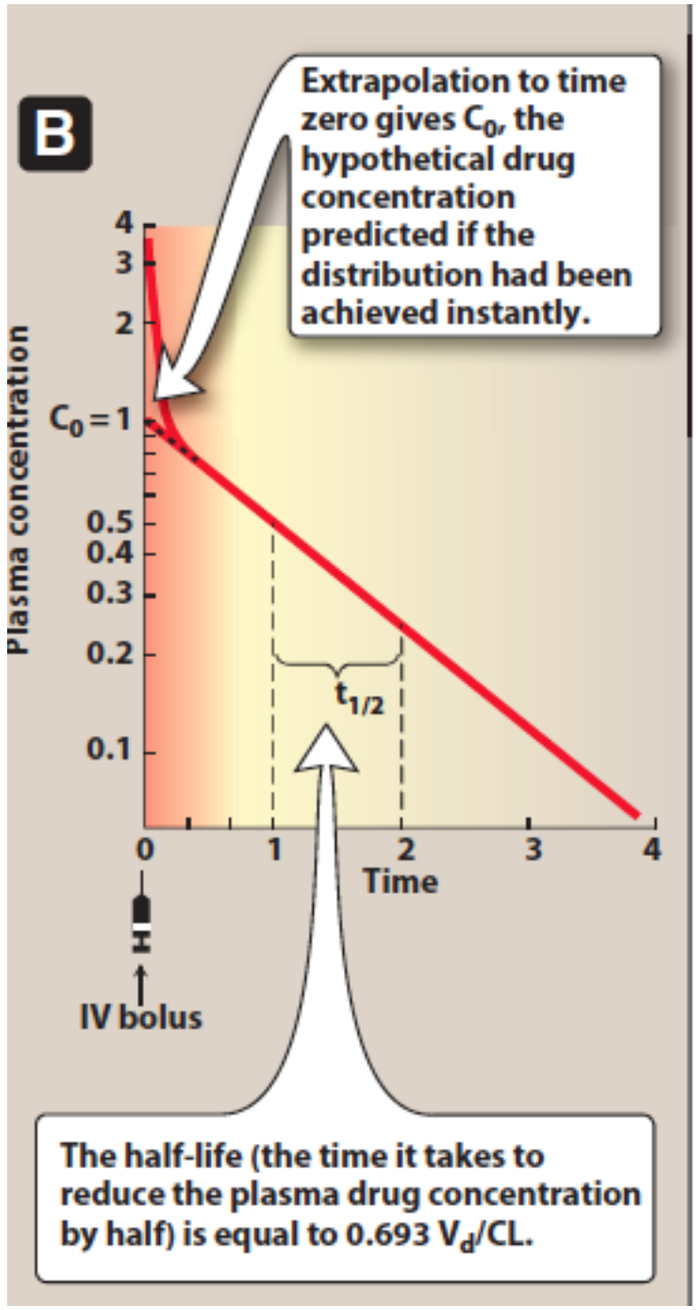
مع انه افتراضي لكن بفيدني بالمقارنة

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

Usually we perform an experiment where we inject a standard dose of the drug wich initially will we injected through IV injection into the bloodstream and this dose will initially be contained entirely in the vascular system.Now this drug will move (start to distribute)to the different compartments of the body(outside of the plasma to the interstitium to the cells) . So the plasma concentration of the drug will decrease with time.



Now we're going to assume that the drug is not eliminated yet. Even though elimination happened at the same time, but just for the purpose of calculation, we're going to assume that the drug is not eliminated. So the drug will achieve uniform concentration that is sustained with time.



يعني أنا ما عندي مشكلة في البسط ، لأنه معروف كم أعطيت المريض دواء ، بس امنيتي انه اعرف كم البسط و هو اللي عشانه بنعمل كل هاي التجربة و الرسمة

We said how do we calculate the volume of distribution? It is the amount of the drug in the body. Now we know this amount because we know exactly how much of the drug we have injected and we gave it through IV administration. So the amount of the drug in the body is going to be 100% equal to the amount of the drug that was injection injected.

بكلّ ذكاء رح تحكيلي C0 عادي بسحب دم المريض اول ما أعطيه الدواء و بشوف كم التركيز ، بس هاد الكلام خاااطئ لانه عند هاي اللحظة كل الدواء اصلاً بالدم ما توزع منه اشي ف الحل الوسط انه نرسم curve بين تركيز الدواء و الوقت ، بالمنطق رح يكون المنحنى متناقص (لانه الدواء عم يروح من الدم لل tissue)
المهم ... عند اللحظة اللي بشوف عندها تركيز الدواء صار صفر بالدم —> يعني بفهم انه الدواء دخل الtissue يعني
✅ distributed
عند هاي النقطة بروح بعمل خط مستقيم يقطع محور الصادات و هاد المقطع هو ال C0 🥳

بعدين بروح بعوّض بالمعادلة اللي بالسلايد الماضي

But how do we calculate C0 or concentration zero? Now, can we immediately take a sample from the patient at the same time we're injecting the drug? Actually, we cannot because the drug will not have started to be distributed all over the plasma. So, what we do? After a drug enters the bloodstream with continued time. So we're going to plot a curve time versus serum concentration. We said we're going to start to see distribution of the drug outside of the plasma to the different tissues. So the concentration of the drug will decrease inside the I vascular compartment.So we're going to draw that curve. But still we don't have concentration zero because the drug has not distributed in equilibrium in the plasma. So after the concentration of the drug reaches almost zero inside the vascular compartment, we're going to plot that curve. It's going to be let's say linear. Then we can draw a line from our curve to intersect with the y axis. And the intersection point between our curve and the y-axis is going to give us concentration zero.
So we're going to figure out what is the concentration at time zero by extrapolation of the curve of time versus serum concentration.After that, we're going to plot that information and we're going to enter that information into the equation and then we can calculate the volume of distribution. إلى صفحة 19

Distribution

- Some areas of the body are not accessible to drugs due to anatomic barriers,
- The capillary membrane between the plasma and brain cells is much less permeable than is the membrane between plasma and another tissue.
- Therefore the transfer of drugs into the brain is regulated by what is called “blood brain barrier”

1. it is only permeable to lipophilic agents
2. impermeable to ionic hydrophilic agents
3. Amino acids, glucose etc have specific uptake systems

ارتباط الدواء بالplasma proteins يعتبر مخزن للدواء depot of the drug و بضل بالدم مدة اطول
الفكرة انه الدواء و هو مربوط بال plasma proteins بكون inactivate و لما يفكّ بصير active ، و أنا عندي balance بين الحالتين

Binding

Remember when we talked about the variable that control the distribution of drug from the plasma to the different parts of the body.
المحاضرة الماضية

- Usually, after absorption, drugs bind to proteins.
- Bound drugs are larger molecules, and therefore can not distribute well and considered as the depot inactive forms of the drug.
- A balance is created between bound (inactive) and unbound (active) forms of the drug.
- Binding can cause drug interactions.

DRUG BINDING TO PLASMA ALBUMIN

- Some drugs bind nonspecifically and reversible to various plasma protein, albumin and globulins, in which the bound and free drug reach equilibrium, and only the free drug exerts a biological effect.

- In general albumin binding reduces pharmacological activity but prolongs duration of action in a way dependent on affinity, binding capacity and rate of dissociation.

continuous but slow release of that inactive drug

- Drug interactions occur on albumin by the displacement of one drug by another. Can raise dose of some drugs to toxic levels.

warfarinال مش مزحة خطير جدا اللعب فيه ، شرحه السلايد القادم

- For example Anticoagulants (Warfarin) can be displaced by the anti-inflammatory agents Phenylbutazone.

Now this depends on different variable.
1. The affinity of that drug to the plasma protein
2. the binding capacity of that plasma protein (how much that plasma protein can hold of the drug)
3. the rate of dissociation between protein and drug

Warfarin : is an anti-coagulant drug. Warfarin binds extensively to albumin inside the circulation.Now this patient usually have a chronic problem, a serious problem. we want to increase the bleeding time in that patient because he have coagulation

إيجابية ال binding انها مخزن للدواء ،، لكن في سلبية : انه رح يصير عندي drug-drug interactions كيف :

عندي مريض باخد warfarin اللي هو anticoagulant ((يعني تخيلوه انه بخلي الدم كتييير زي المي 🫠))
بالحالة الطبيعية هذا الدوا ماسك بال albumin و الوضع تمام
لكن راح المريض اخد دواء آخر برضو يرتبط مع ال albumin!!
اسمه phenyl butazone (anti inflammatory)
ف صاروا الدوائين يتنافسوا على ال albumin
ف كمية الwarfarin اللي (مش مرتبطة) عالية ←— يعني الدواء كتييير active ((يعني الدم كتيير 🫠))
ف مجرد جرح صغير الدم رح يطلع بسرعة it could be fatal !!

ف لازم تكون تعرف هاي الأمور عشان تقرر بديل
للدوا و تقرر الdose اللي تعطيه

Protein-binding

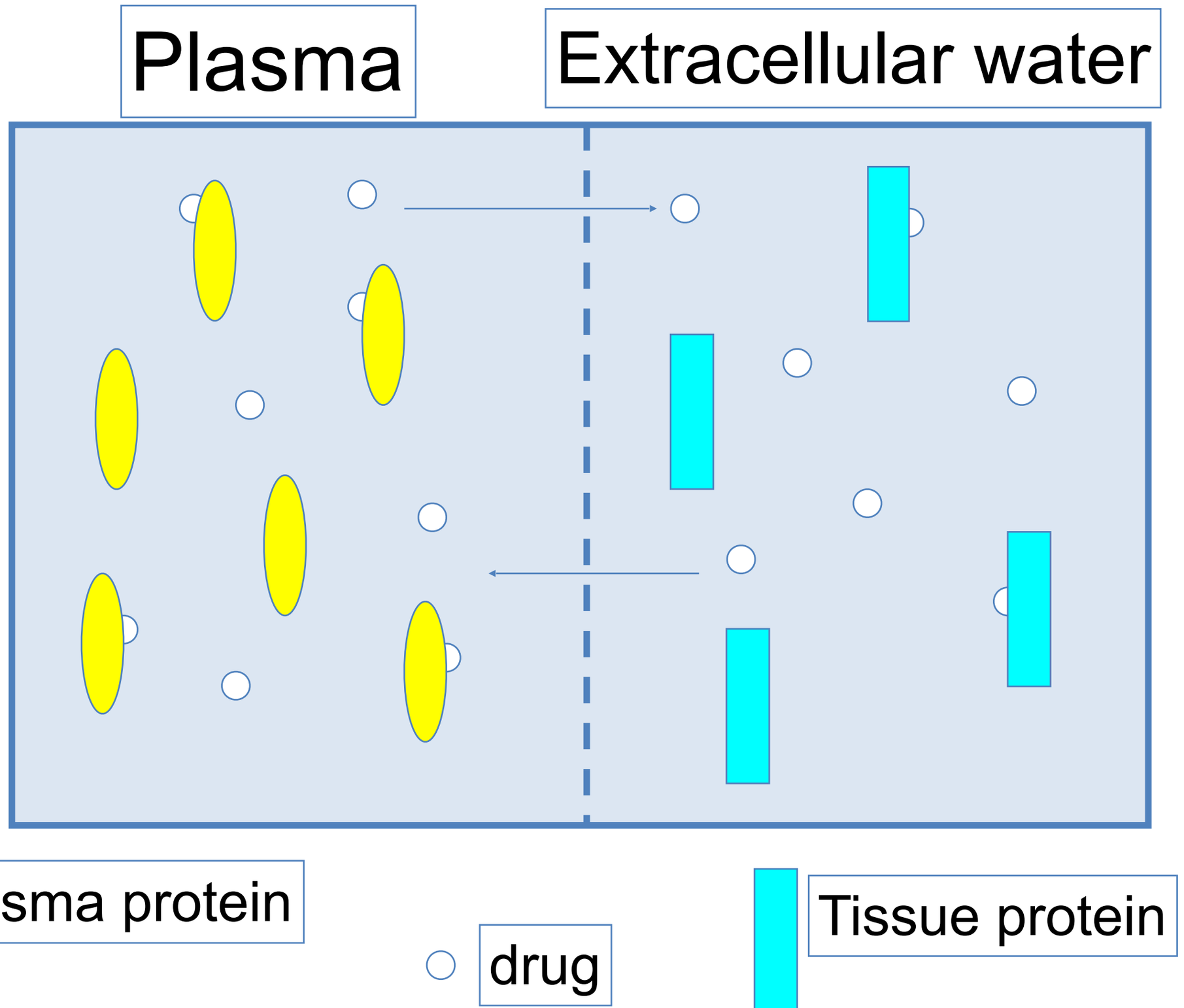
- Only unbound drug is capable of crossing the placenta
- Drugs with low protein binding reach higher concentrations in the fetus than mom

Protein binding

- not only **affects the activity** of the drug (bound = inactive)
- But also can **influence its distribution** from one compartment to another.
- This is particularly true with respect to **glomerular filtration** and **passive transport**.

شوفوا الرسمة بالصفحة التالية
انه بس ال free drug بقدر يمر

Free Drug + Protein ⇔ Bound Drug


Plasma
Extracellular water
Plasma protein
drug
Tissue protein

Plasma Proteins

albumin

- primarily for acidic dru

a_1-acid glycoprotein

- for basic drugs

Lipoproteins

- for some drugs Lipid soluble drugs

The fraction of total drug in plasma that is bound is determined by

- **the drug concentration,**
- **its affinity for the binding sites, and**
- **the number of binding sites.** Capacity

Volume of Distribution (Vd)

How can we measure the extent of distribution?

Apparent volume of distribution (V_d)

$$V_d = \frac{\text{amount of drug in body}}{\text{plasma drug concentration}}$$

هل انت في بجسمك 140L
لا طبعا في بالجسم 42L
و هاد اللي كنا نحكيه ، انه هاد الرقم افتراضي hypothetical volume

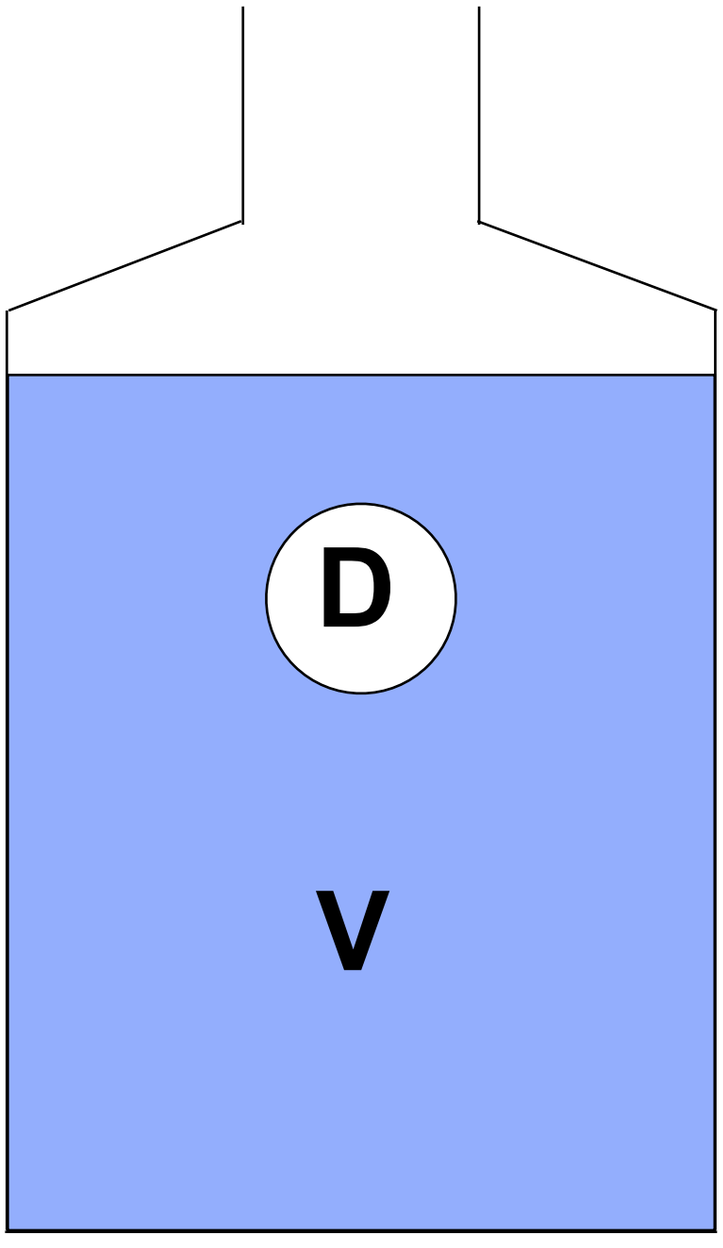
VOLUME OF DISTRIBUTION FOR SOME DRUGS

DRUG	Vd (L)
cocaine	140
clonazepam	210
amitriptyline	1050
amiodarone	~5000

اللي بكون الها ال drug distribution عالي جدًا زي ال amiodarone بنفهم انه:

this drug is probably localized inside certain tissues or it's completely got trapped inside the cell
very little of this drug is present in the plasma

Volume of distribution

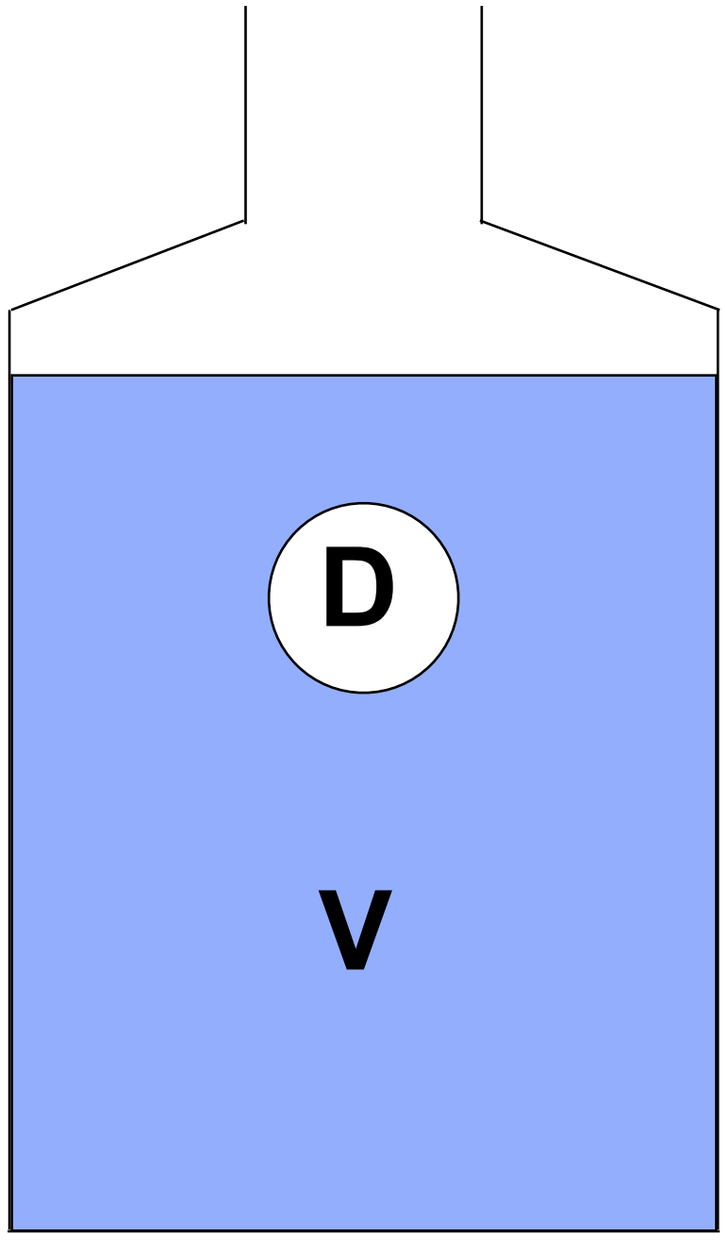


$$C = D/V$$

$$V = D/C$$

Volume of distribution - an example

That you might have in the exam



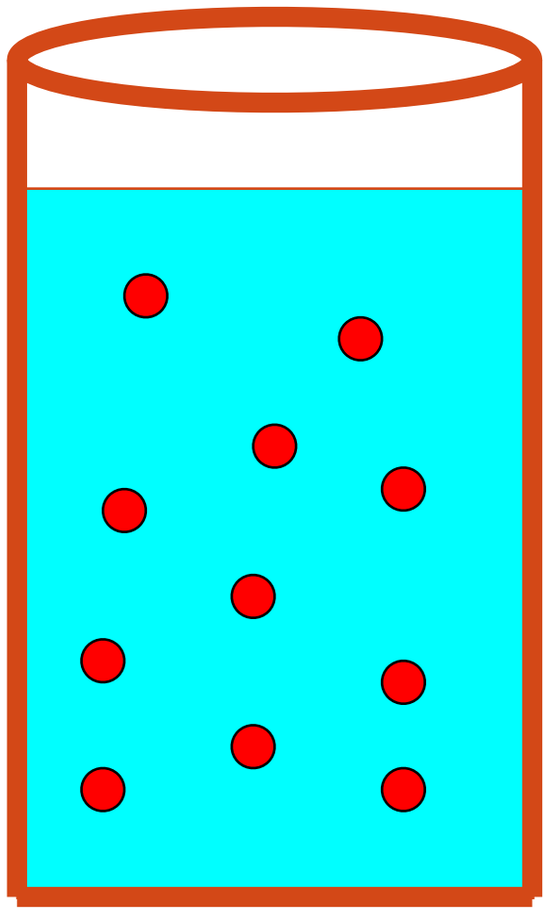
D = 50 mg

C = 2.5 mg/L

V = D/C

= 50mg / 2.5mg/L

= 20 Litres



What is the volume of water in the beaker?

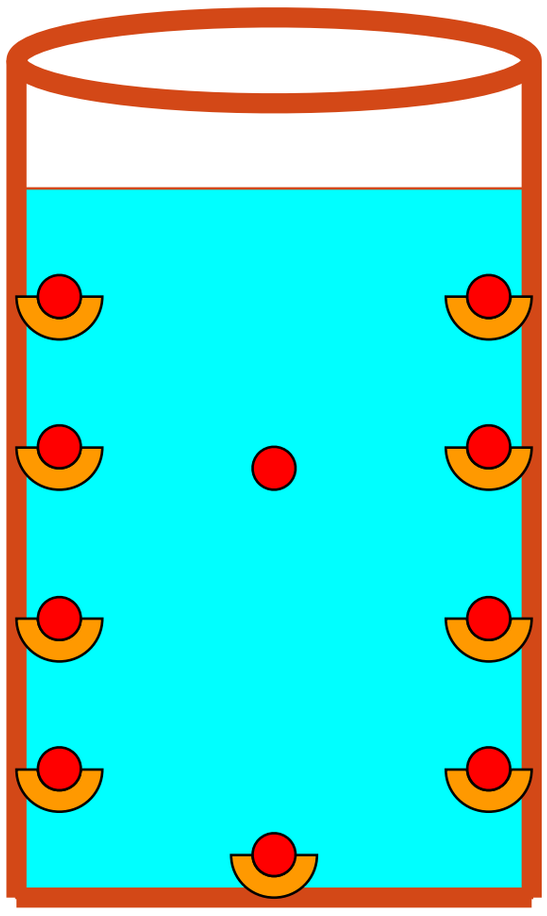
$$\text{Volume} = \frac{\text{amount}}{\text{concentration}}$$

$$\text{Volume} = \frac{\text{10 mg}}{\text{10 mg/L}} = 1L$$

الحبّات

I hope this simple example can explain the concept of volume of distribution.

water gets distributed or localized to other places in the beaker which are depicited in those little saucers that we drew here. So water got distributed to the different parts of this beaker which represent the different places where the drug is distributed in our body. So some of that water molecule got attached to the muscle, some of it to the lipids, some of it got inside the cells. So the amount that can be detected of water inside the beaker or we represented by that in the plasma is one molecule.



What is the volume of water in the beaker?

$$\text{Volume} = \frac{\text{amount}}{\text{concentration}}$$

$$\text{Volume} = \frac{10mg}{1mg/L} = 10L$$

And this is not the real volume because we still know that this beaker has a volume of one liter. And this is what we mean by an apparent volume.

So if I want to calculate the volume of water in the beaker now we know again that the volume equals the amount divided by the concentration.السلايد الماضي
Still the amount of water الحبّات in the beaker is the same. We know we put 10 mg of water in that beaker. But what about the concentration? If I take a sample of that beaker now, I'm going to get a concentration of 1 mg per liter because all the other water molecules got distributed elsewhere.

Volumes of distribution (Vd)

(In litres for average 70 Kg adult human)

So this is a characteristic in identifying parameter for drugs in order for us to be able to conclude where the drug is distributed in.

Warfarin	7
Gentamicin	16
Theophylline	35
Cimetidine	140
Digoxin	510
Mianserin	910
Quinacrine	50,000

Small vol. Mainly stays in plasma little in tissues.

Medium vol. Similar concs in plasma and tissues

Large vol. Mainly in tissues, little in plasma.

ارجعوا لصفحة ١٠

Volume of distribution and body weight

Vd depends upon body size.

May be quoted as L/kg (Litres per kg body weight)

e.g. Theophylline Vd = 0.48 L/kg

For 60 kg adult, Vd = 0.48 L/kg x 60 kg

= 28.8 L Standard is : Liter

So it's going to be different for each individual.

Practice calculation

الفكرة بال mixed units يعني وحّدهم

A dose of analgesic (50mg) is administered i.v. and a blood sample is taken shortly afterwards. The initial concentration of analgesic in the blood sample is 0.85 μg.ml^{-1}.

Calculate the volume of distribution of the analgesic (in Litres).

Model solution

Mixed units!

$$V = D/C_0$$

$$= 50 \text{ mg} / 0.85 \mu\text{g.ml}^{-1}$$

$$= 50{,}000 \mu\text{g} / 0.85 \mu\text{g.ml}^{-1}$$

$$= 58{,}824 \text{ ml}$$

$$= 59 \text{ Litres}$$

Metabolism

موضوع جديد ، الجزء الأخير من المحاضرة

- Drugs can be broken down(metabolized) in the body by various mechanisms.

Changes the structure

- Metabolism usually results in compounds which can be excreted.

احنا بنعرف انه اغلب ال excretion للدواء يكون خلال ال kidneys
يعني in urine يعني لازم يصير water soluble و هاد جزء من
هدف ال metabolism

- Metabolism can:
  - Inactivate the drug Most commonly happens
  - But sometimes Activate the drug
  - Produce other active metabolites.

Metabolism

- Liver is the major site for drug metabolism. Biotransformed
- Also, the kidneys, the g.i.t, plasma, and lungs can metabolize drugs.

بس اقل من ال liver

- Metabolism can be affected by:
  - Disease state. liver cerosis: part of his liver is not functioning.
  - Blood flow. طردي
  - Inducers and Inhibitors. لما أعطي دوائين او اكثر Drug drug interactions رح نحكي عنها كمان شوي
  - Genetic background of the patient. ⤵
  - Tolerance.

pharmacodynamics اقرب لل

في ناس جيناتهم بتصنع إنزيمات بتكون fast in metabolism بنسميهم rapid metabolisers , و النوع الآخر slow enzymes ف بنسمي المريض slow metaboliser

So choosing the proper drug and choosing
the correct dose of the drug for these patient will be different.

Metabolism

- The liver is the major side of metabolism for many drugs, but other organs, such as lungs and kidney can also metabolize drugs.

يعني أنا بالmetabolism هدفي الأساسي ليس تحويل الdrug إلى inactive form مع ان هذا يحصل بس مو هو الهدف الأساس
إنما الهدف الأساس هو تحويله إلى conjugated so more polar

- Many lipid soluble drugs are not readily eliminated from the body and must be conjugated or metabolized to compounds that are more polar and less lipid soluble before being excreted.

- Metabolism often, but not always, results in inactivation of the compounds.

- Some drugs are activated by metabolism, these substances called prodrugs.

a drug that's given in its form being inactive. It needs to be metabolized in the body for it to become activated and perform its activity.
But this is as we said a small percentage of drug and most of the time metabolism results in inactivation of the drug.

Phase I metabolism

- Drug metabolism occur in two phases:
- Phase I reactions function (e.g., oxidation, reduction, hydrolysis) alter chemical reactivity and increase water solubility.

phase one reactions function to convert lipopilic molecules to a more polar molecule by introducing a polar functional group suchOH or NH2.

- Phase I reaction frequently catalysis by the cytochrome P450 system (also called microsomal mixed function oxidase).

$$\text{Drug} + O_2 + \text{NADPH} + H^+ \rightarrow \text{Drug}_{\text{modified}} + H_2O + \text{NADP}^+$$

- To date, 12 unique isoforms of this enzymatic system (CYP 2D6, CYP3A4) have been identified to play a role in human drug metabolism.

So the oxidation proceeds by the drug binding to the oxidized form of cytochrome P450. As you can see we need oxygen in the reaction and then we have a reductive step coupled to NADPH cytochrome P450 oxoreductase.

we have several isoforms of cytochrome P450 enzymes. To date we have12 unique isoforms of the enzymatic systems and these are called SIP , examples here: SIP 2D6 SIP 3 A4 which have the highest role in metabolizing drugs utilized by human.

Phase II metabolism

- If the metabolite from phase I is polar enough it will excreted by the kidney, But if it is still lipophilic to be retained in the kidney, a subequence Phase II metabolism will take place.

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

- Results in polar and usually more water soluble compounds.

Cytochrome P450 system

هذا موضوع مهم جدًا لأنه بصير عليه drug drug interactions , بتتذكروا لما حكينا عن inhibitors and inducers قبل اكم سلايد ؟

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

الشرح الصفحة القادمة

- Cytochrome enzymes Inducers like Rifampin (Anti biotic) and Carbamazepine (Used Centrally) are capable of increasing the synthesis of one or more of isoforms (Of cytochrome enzymes). For example, Rifampin significantly decreases the plasma concentration of HIV protease inhibitors. (Are metabolised by cytochrome p450)

هذا الدواء باخذه مريض ال AIDS HIV أصلا

الشرح بالصفحة اللي بعد القادمة

- Cytochrome enzymes inhibitors, Omeprazole inhibits three CYP isoforms that are responsible for Warfarin metabolism, leading in an elevation in the Warfarin concentration, and so greater inhibition of coagulation, leading in to more risk of serious bleeding reaction.

ف إذا اجيت و أعطيت هاد المريض (الأدوية اللي بالأصفر اللي بتزيد تصنيع ال p450) رح يزيد الmetabolism للدواء الأصلي اللي أنا بعطيه لمريض الAIDS (اللي هو الدواء اللي بالأزرق) ف المريض عم بعمل metabolism اسرع مما هو بياخد اصلاً !!! ف كإنه مش قاعد بياخد دواء ، يعني تركيز الدواء بالدم غير كافي لإعطاء اثر

This will result in decreasing the plasma concentration ofthe HIV protease inhibitor which can lead to having a plasma concentration that
is lower than the effective minimum effective concentration therapic effect. So the patient is taking a drug to treat a serious condition and heal aids but the drug is being metabolized in his body. So it's not performing its action. So this is very important.

Omeprazole is a drug given to treat peptic ulcer
بس الناس بياخذوه بطريقة غلط يعني over the counter يعني بدون ما يستشيروا طبيب عشان يعالجوا مشاكل بالمعدة ، مثلاً واحد ثقّل بالأكل او اكل heavy or oily meal ف بقرر لحاله انه ياخد هذا الدوا ، و فعليًا رح يخفف حموضة المعدة ، طيب شو الخطر ؟؟؟
بكون المريض اصلاً بأخذ warfarin و الطبيب واصفله اياه بالdose المناسب اله ، هلأ لما يقرر من حاله ياخد omeprazole اللي بممنع تصنيع cyp يعني رح يممنع ال metabolism تبع ال warfarin ف الجسم مش قاعد يتخلص من ال warfarin ف بضلّ بالجسم بتركيز اعلى (ف بصير الدم كتيير 🫠) elevation of warfarin concentration in the plasma

⛔It is very serious to miss up with the concentration of Warfarin in the body

Elimination

- It is a process in which drugs are transferred from the internal to the external environment.
- Occur via a number of routes , the most important being through the kidney into the urine.
- Other routes include the bile, intestine, lung, or milk in nursing mother.
- Drugs eliminated through these routes tend to be lipid soluble and unionized.

اللي غير ال kidney

elimination can happen through different rates depending on the kind of drugs. It can happen through different kinetic process. We have zero order kinetics and first order kinetics as an example.

Elimination

- **Zero order:** constant rate of elimination irrespective of plasma concentration. يعني شو ما تزوّد عيار الدواء ،ما بفرق معي ، أنا عندي رقم محدد من ال transporters هم اللي بشتغلوا
- **First order:** rate of elimination proportional to plasma concentration. Constant ***Fraction*** of drug eliminated per unit time. كل ما يزيد تركيز الدواء بزيد ال distribution و هو الأشهر

In zeroorder kinetics we have a concentrate of elimination irrespective of plasma concentration.
So in this case if we have the drug elimination dependent on certain transport mechanism that help the drug gets from the circulation into the urine. We have certain transport protein again these are saturable protein that will only take a certain amount of drug to transport it. Now because it is a saturable process it will depend on the number of transporters available in the kidney but they will not depend on the concentration of the drug. In this case we have a zero order kinetics

Rate of elimination ∝ Amount

Rate of elimination = K x Amount

Now first order kinetics : the rate of elimination is proportional to the plasma concentration which is the most common route or that happens usually. So we have a constant fraction of drug eliminated per unit time depending on a certain constant called K.

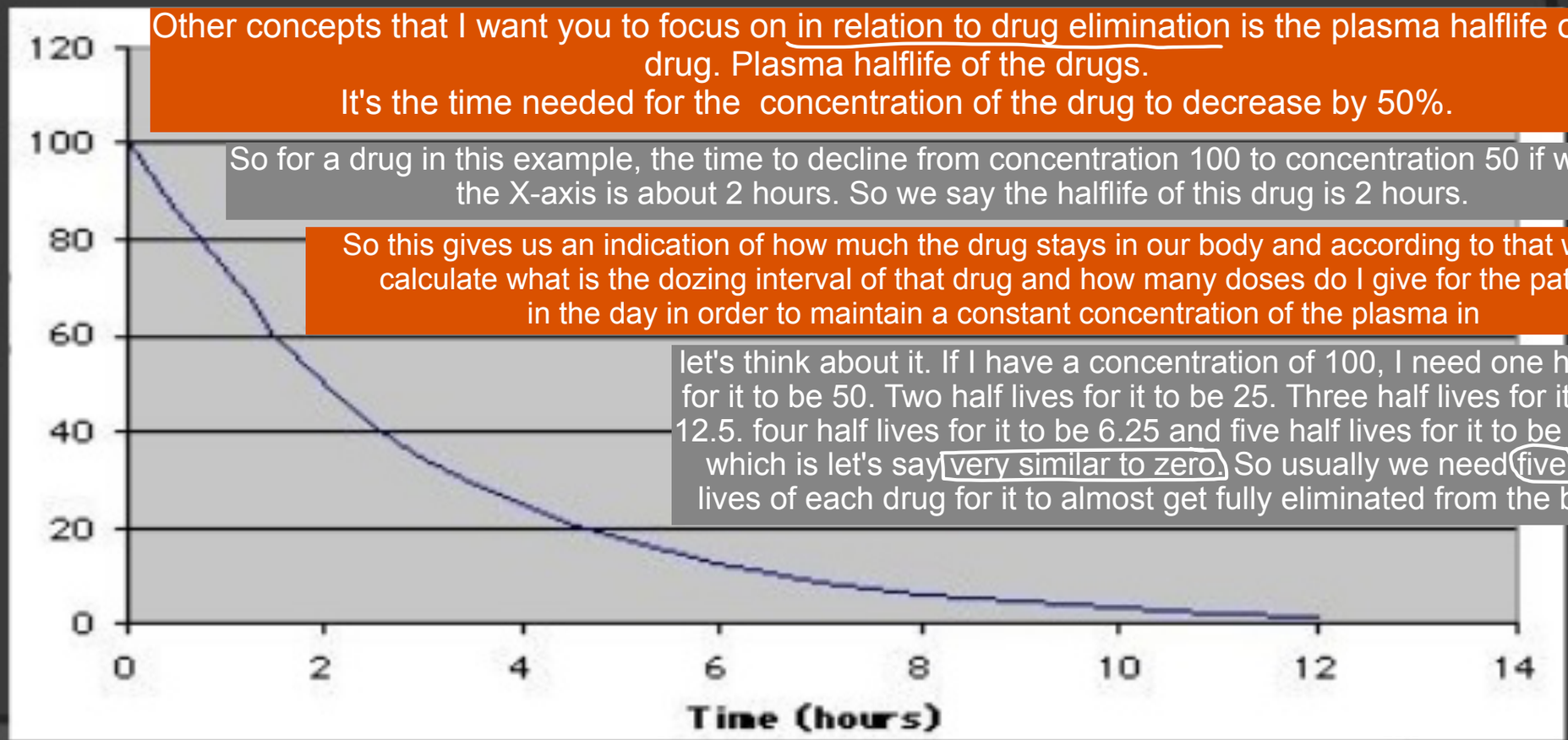
Elimination

- Drugs can be eliminated through various routes (kidney, lungs, sweat, feces).
- Metabolism usually results in inactive metabolites which are also water soluble and therefore excretable by the kidneys.
- Weak acids are excreted faster in alkaline urine.
- Weak bases are excreted faster in acidic urine.
- Elimination follows first-order kinetics of decay.

Plasma half life ($t_{1/2}$) of drug

$$t_{1/2} = \frac{0.7 \times V}{CL}$$

- Time to decline conc. from 100 to 50 = 2 hr
- So, $t_{1/2}$ of this drug is 2 hr



Other concepts that I want you to focus on in relation to drug elimination is the plasma halflife of the drug. Plasma halflife of the drugs.
It's the time needed for the concentration of the drug to decrease by 50%.

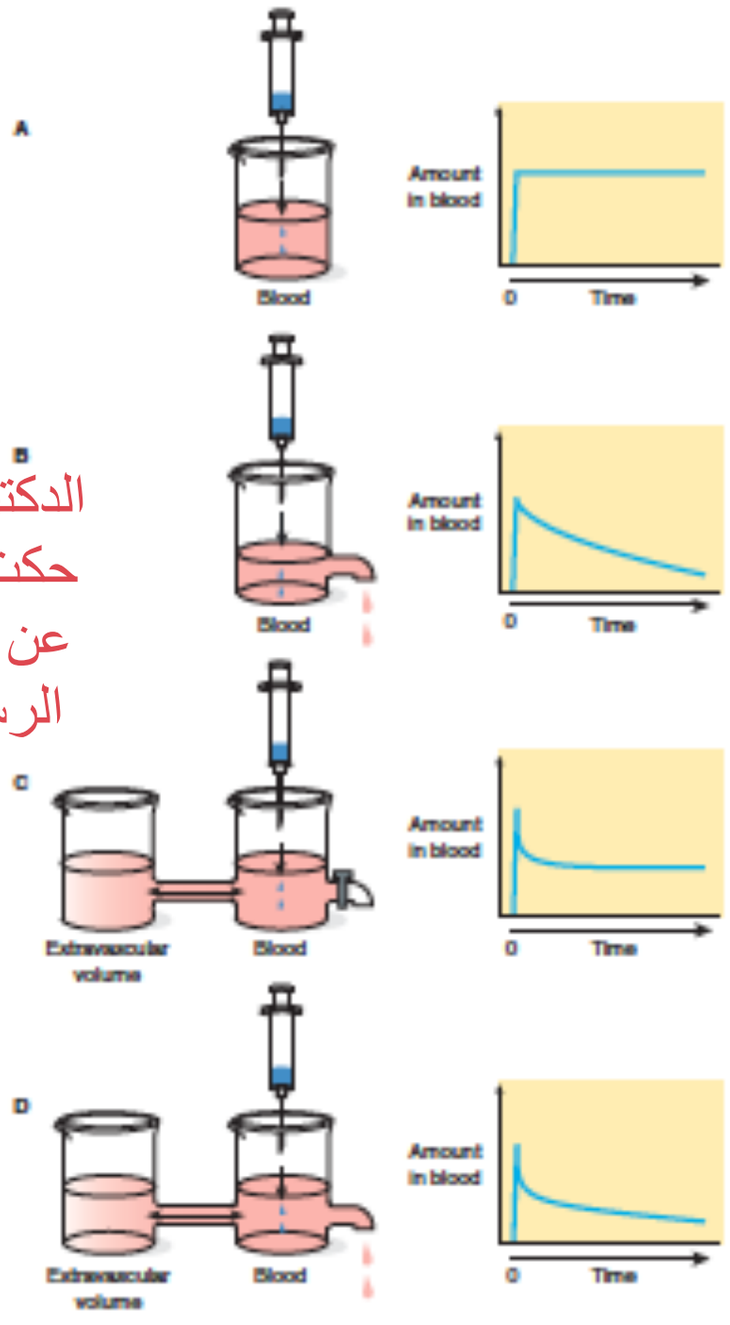
So for a drug in this example, the time to decline from concentration 100 to concentration 50 if we look at the X-axis is about 2 hours. So we say the halflife of this drug is 2 hours.

So this gives us an indication of how much the drug stays in our body and according to that we can calculate what is the dozing interval of that drug and how many doses do I give for the patient in the day in order to maintain a constant concentration of the plasma in

let's think about it. If I have a concentration of 100, I need one half life for it to be 50. Two half lives for it to be 25. Three half lives for it to be 12.5. four half lives for it to be 6.25 and five half lives for it to be 3.125 which is let's say very similar to zero. So usually we need five half lives of each drug for it to almost get fully eliminated from the body.

Clearance: pharmacokinetic measurement of the volume of plasma from which a substance is completely removed per unit time; the usual units are mL/min. The quantity reflects the rate of drug elimination divided by plasma concentration.

So this is different than the halflife. The half-life is the time while the clearance is the volume of plasma.



الدكتورة ما حكت اشي عن هدول الرسمات

$$CL = \frac{\text{Rate of elimination}}{C}$$

And it will depend on the rate of elimination of the drug and the concentration of the drug.

Of course, depending on which order kinetics the drug is eliminated by.

كان شيخ الإسلام ابن تيمية يسعى في حوائج الناس سعيا شديدّا لأنه يعلم انه كلّما أعان الناس أعانه الله

- كتاب روضة المحبين/ ابن القيّم