Pharmacology

Sheet Slide

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Routes of Drug Administration

II. Parenteral routes:

1.Intravenous (IV):

Disadvantages:

- **Irreversible:** hard to stop its reaction but in some cases it could be reversed by **antidote**. This means that it's not irreversible 100%.
  Antidote: a medicine taken or given to counteract a particular poison, after overdosing or after taking a wrong medicine, unpredictable side effects.
  (it's not available for each medicine)
  For example "**Don't save**" :
  heparin antidote is protamine sulfate
  paracetamol anti dote is N-acetylcysteine
  - then we try to avoid IV due to its high risk, toxicity, irreversibility, fast appearance of side effects. Due to it's fast delivery to blood and body tissues (fast absorption) in contrast with the oral route where drug absorption in the GI is gradually gradually appearance of side effects.
- May introduce infection at the site of injection.
- It can coagulate through interaction with the substances that already are present in the blood.

Note: Side effects differ between individuals: How?
Example: a drug that causes tachycardia as a side effect; may cause a predictable increase in the heart rate of a patient.
On the other hand, it may cause higher and unpredictable levels of heart rate > sudden arrhythmia > heart attack > death.

-IV can be divided into two type :
1.**IV Bolus**: rapid injection, fast effect, short duration of action, fast absorption.
2.**IV Infusion:** is the supply of fluid by drip, used to avoid bolus disadvantages, when we need to avoid toxicity, high risk and to get long duration of action.

2. **Intramuscular (IM):**

-rapid absorption of drugs (slower than IV), divided into:

1. **Rapid** IM injection: drug is dissolved in aqueous media (polar) fast absorption.

2. **Slow** IM injection: **depot** injection: drug is not dissolved in aqueous solution "thick oily media such as polyethylene glycol for example" slow action (similar to orally Extended release)

In Each route we have slow and rapid (rapid is relatively rapid).

3. **Subcutaneous (SC):**

As Insulin, Minimizes the risks of hemolytic or thrombosis associated with IV injection.

III. Others

1.Inhalers:

- can be given for:

1.systemic effects: when it's acceptable.

2.local effects: to treat lungs diseases such as **Asthma**

most studies shown that it's better to treat **Asthma** using oral inhaler to avoid reaching systemic circulation to avoid systemic side effects.

local inhaler reach the lower respiratory track to alveoli (**Asthma**)

 reach the upper respiratory track (Nasal inhalation). Such as mometasone furcate which is used for allergic rhinitis.

2. Intrathecal/ intraventricular:

Introduces drugs directly into cerebrospinal fluid, high risk, high probability to cause paralysis

It may be diagnostic: to analyze a cerebrospinal fluid sample it's necessary since it is the only way to take the sample.

or for treatment: it's dangerous so in most states we avoid this route in some cases we need to use it when:

Drugs cannot cross the blood-brain barrier to the CNS. Notice that when the drug can't cross the blood-brain barrier we look for another drug that can be administrated by other routes (can penetrate the blood-brain barrier) that are less dangerous, whether the other drug is less effective. Then we think about giving the drug in the Intrathecal way.

هون الموضوع مش لعبة و مش سهل صراحة أنه يعطى لذلك الدكاترة عم يحاولوا يجيبوا دوا بديل بنفس القوة و يفيد المريض ان ما لقوا بحاولوا يلاقوا دوروا ع دوا أقل قوة منه و يحاولوا تحت أي ظرف ما يستعملوه الا كحل أخير لما ما يظل ولا أي حل قدامهم و يكون الشي الوحيد الي قدامهم هو أنهم يتركوا المريض يموت فيستعمون هذه الطريقة

3.Topical:

skin dermal: local action target (skin)

 transdermal: systemic action use skin to reach the systemic circulation such as the nicotine patch, nitroglycerin patch for angina (transdermal absorption differ according to the place on an (Extensive circulation or non-extensive circulation) * the best places for absorption are in shoulder, flanks, abdomen.

Pharmacokinetics

Pharmacological effect: (therapeutic effect or side effect)

Pharmaco=drug, kinetics= movement

Pharmacokinetics: What the body does to the drug.

1-Absorption.

2-Distribution.

3-Metabolism.

4-Elimination.

***Why do we study pharmacokinetics?**

There are some factors that affect the therapeutic effect of the drug, every individual has his internal & external conditions so we will know the correct drug, correct dose and correct duration for the correct patient.

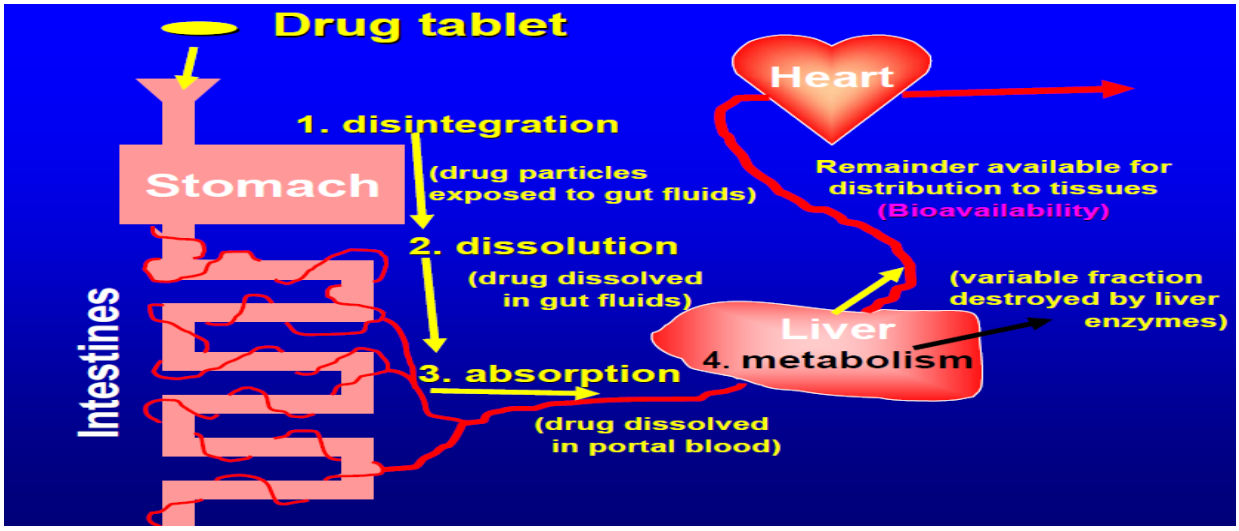
The pharmacokinetic properties of a drug determine:

1. Onset of drug action 2. Intensity of the drug's effect 3. Duration of drug action

These goals determine: 1-ROA. 2-Dose & frequency. 3-Duration. (Best therapy)

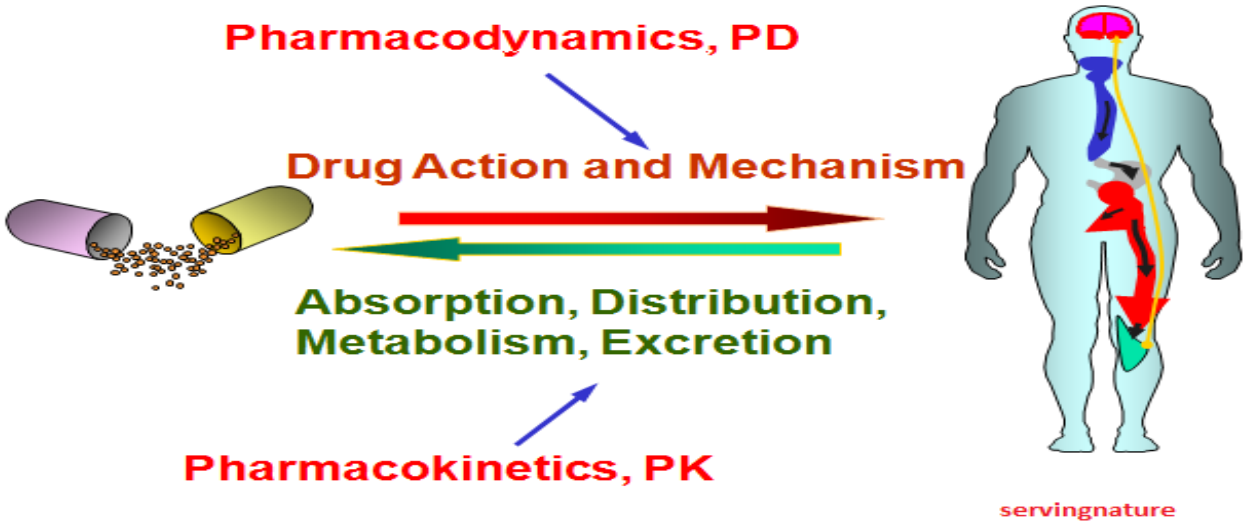
>>administration of drug tablet (disintegration)dissolution absorption by portal vain liver metabolism under the name of first past effect the rest of the drug goes to blood (systemic circulation)
*if high amount of the drug reach the blood drug can be given orally
* if low amount of the drug reach the blood drug can't be given orally. (looking for other effective routes, IV, IM, topical, sublingual, "partially rectal")

يعني لو الدواء بده يتكسر و أخسره لليش أخلي المريض يدفع عليه مصاري و في الآخر يروح الجسم ما يستفيد منه !!



-pharmacodynamics includes chemical reaction of the blood and side effects.

تخيلوا عندي طوشة بين الجسم و الدواء الضربات الي بيضربهم الجسم بسميهم كاياناتكس و الضربات الي بيضربهم الدواء داينامكس



ABSORPTION OF DRUGS:

Studying the absorption of the drug can give us a hint for the onset of action & we can approximately know the effective concentration in the body so we can know the intensity of the drug effect & duration of action. (monitoring for the patient)

Absorption: transfer of the drug from the site of administration until it reaches the general circulation.

Variability of absorption due to ROA:
IV -----> NO absorption **"القصد ليوصل يوصل للدم"**
IM ----> Muscle – Blood stream
Oral (most variable route) ----> oral cavity – GIT – Portal vein- liver – General circulation
GI barriers + Portal vein circulation affect the oral route; it varies between individuals.

<u>Absorption is determined by two parameters:</u>

1.Rate: The needed time to reach the maximum concentration (peak) of the drug in the plasma or how rapid speed of absorption (it's not very Important in oral route) such as Cl supplement. But it's important in IM and IV.

2. Extent: how much (**bioavailability**= F) , F= **<u>fraction</u>**.
It`s the amount of the drug that reach the general circulation = **all amount / amount that reach to blood**
ركز هوون مش بالأغنية إلي بتسمع فيها "لا وحدة لها و يعبر عنها على صورة بسط و مقام "

*Rate & extent calculated in the labs.
* Oral route: At T0 ---> drug concentration in the plasma=0

- The two parameters depend on:
  1. the environment site of absorption, acidity in stomach. (related to absorption ability as "food drug interaction).

  2.the physiochemical properties of the drug (MW/Ionization/...)
  For e.g. Very lipophilic drugs adhere on the membrane.

  3.Route of administration (bioavailability). "IV=100%, oral (0-~100)% IM for the same drug may be more than oral also subcutaneous

- in some conditions all these factors may improve the absorption of some routes and decrease the absorption in other ones

Bioavailability: it refers to the degree and rate at which an administered drug is absorbed by the body's circulatory system. It's a fraction
Example 50mg of a 100mg reach the blood circulation bioavailability=0.5

notes:
*Bioavailability is important to determine: 1-Dose. 2-ROA.
Eg. The effective concentration of drug X is 200mg, its oral bioavailability=60%, calculate the dose:

200/(dose)=60%
Dose = 333.3 mg

جماعة هاد مثال توضيحي مش مطلوب مننا لذلك ما حد يحفظه
و صحيح ما حد يستعمل الكتلة للحسابات لازم نستعمل التراكيز

**Sometimes we can't control the low bioavailability of the drug, we can't control the large amount of the drug in the GIT, it may cause local side effects.

Figure:
- Three drugs A, B, C in the same rout oral for example.
- Y-axis amount of the drug in the blood.
- X-axis: Rate.
- A has the higher extent of absorption according to (F): A>B>C. Then A is more Bioavailable than B, C.

- According to Rate: the three of them reaches the maximum value at the same time.

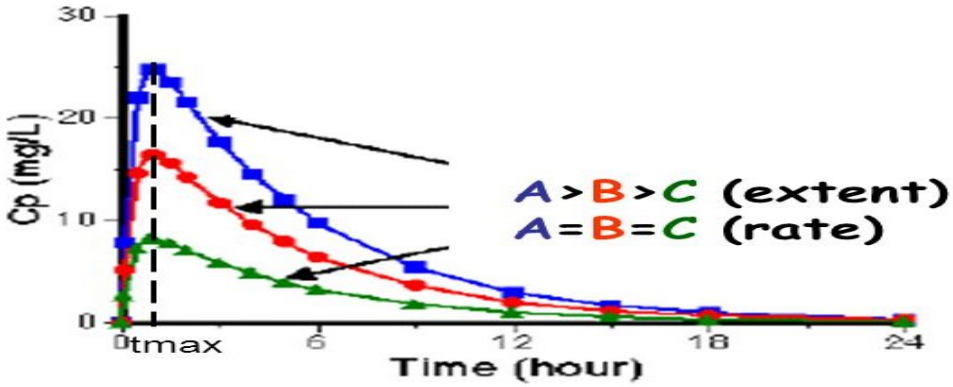


Figure:

- A,B,C Three different oral formulation of the same drug for example tablet ,capsule..
- Extent:
  -A is the most bioavailability
  -B and C are comparable, because they are in the same therapeutic effect.

Rate: A=B maximal effect at the same time C slow rate.

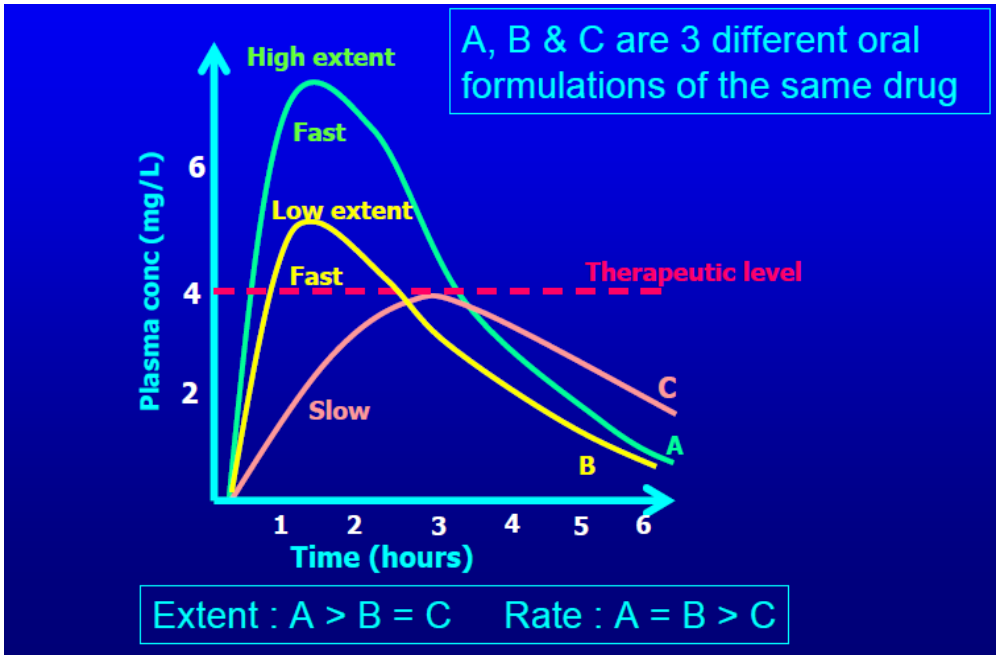
Notes:

The most appropriate drug is B (Yellow curve).

A (Green) may be an overdose.

We can consider that 1-"A" may be IM inj. 2-"B" may be syr. 3-"C" may be cap.

Form of the dose influence absorption: Solid dosage forms (capsule, tablet) must be dissolved before absorption.



Mechanisms of absorption of drugs from the GI tract

نفس الي أخذناهم بالفسيولوجي بالزبط "دواء أو أكل ما بيفرق على الخلية بالحالتين اسمهم مواد من برا الخلية".

1.Passive diffusion (simple diffusion): with concentration gradient (from high concentration to the lower concentration)

*No need of energy

**Simple diffusion: Small molecules:

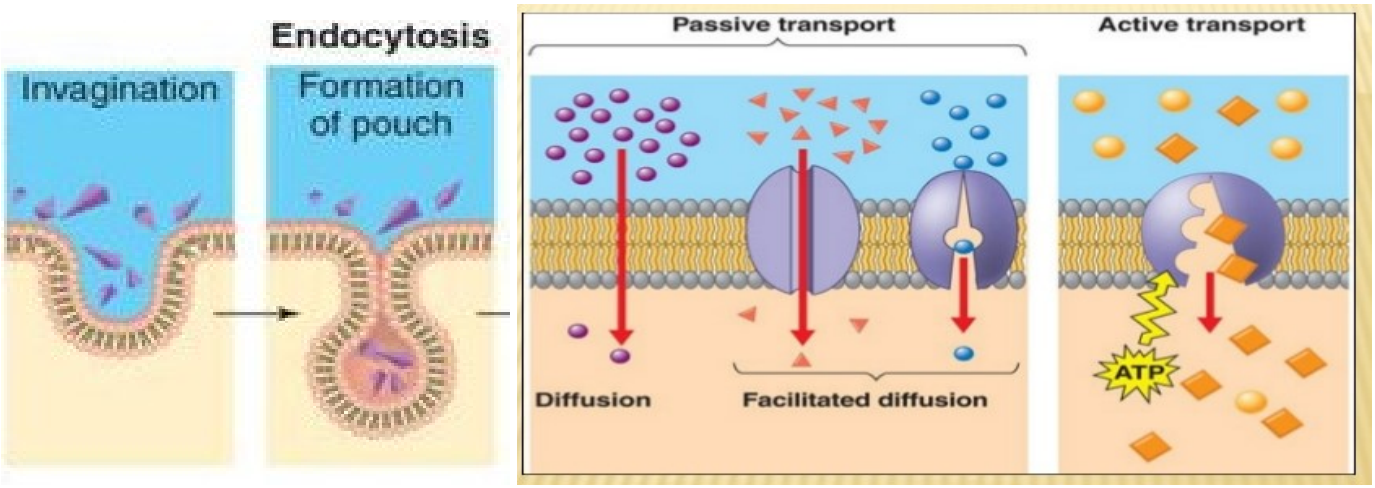
-Water “aquaporins”

-Lipid soluble molecules “membrane”

2.Facilitated diffusion: with concentration gradient need a facilitator protein (transport protein).And it doesn't require energy. **Large** amount of water goes inside the cell by facilitated diffusion.

3. Active transport: used to transport the drug against concentration gradient (from low concentration to the higher concentration), needs energy + carrier proteins .

4. Endocytosis: used with large molecular-weight drug such as B12 vitamin and norepinephrine, it's a physical way for a drug entry, needs energy.



Selectivity: there is a substrate for each carrier. (Active transport is highly selective"موضوع عليه دفع مصاري")
Competitive inhibition: an inhibitor that resembles the normal substrate binds to the carrier protein and prevents the substrate from binding, so higher affinity will inhibit the receptor. (Maltose-glucose inhibition)
Saturation: cell can take a specific amount of the drug.

*Competitive inhibition & saturation are found in passive & active transport and these properties may lead to: Food-Drug interaction/ Drug-Drug interaction

- **Factors affecting the absorption:**
  (especially for oral route)

  1.May be related to the environment: Effecting of PH stomach. Unchanged (neutral) drug can pass readily through membranes but uncharged ones cannot.

  PH: -Acidic medium in the stomach
  -Basic medium in the intestine
  -Any substance must be neutral to be absorbed
  -Any charged substance will stay in the lumen of the GI
  -Drugs are either weak acids or weak bases
  -Weak acids: HA (protonated form will be absorbed)
  HA <----> H+ + A-
  The drug will be effective in acidic medium so we need to control the reaction to produce HA form (Acidic medium will increase H+ conc. So, the reaction will go to the left), **Acidic drugs are better absorbed in the stomach.**
  -Weak bases: B (deprotonated form will be absorbed)

B + H+ <----> HB+
The drug will be effective in basic medium so we need to control the reaction to produce B form (deprotonated neutral) , (Basic medium lack the H+ this condition will lead the reaction to go to the left forming B form of the drug), **Basic drugs are better absorbed in the intestines.**

2.High blood flow high level or (favored) of absorption in intestines than in the stomach (also it differs between individuals)
>> in the GI, drug may be absorbed in stomach & intestines.
Intestines are the preferable site of absorption (Rich supply of blood capillaries)

3.Total surface area available for absorption: Intestines are the preferable site of absorption (Large surface area + Microvilli)

4.Contact time at the absorption surface: Emptying an empty stomach is faster than emptying a full one, so acidic drug is better to be administered on full stomach (to increase the contact time with stomach + food will stimuli the acidic enzymes to be secreted), Basic drug is better administered on an empty stomach.

5-P-Glycoprotein (PGP):

P-GP carrier/transporter

-Found in blood capillaries in the intestines/epithelial tissue of the intestines/ BBB / Placenta / Nephrons /...

-Prevents absorption of some toxic substances (if this substance is a substrate for the P-GP) : A pump that pump out substances from the epithelial cells in the intestines back to the lumen of the intestines.

If the drug is a substrate for the PGP its bioavailability will be low if the PGPs are active. (Inverse proportion)

Infection increase PGP numbers.

Some drugs increase/inhibit PGPs which lead to Drug-Drug interactions

Bioavailability

بالمختصر هي قديش الكمية إلي وصلت للدم من الدواء

It is the rate and extent to which an administered drug reaches the systemic(general) circulation.
Example:

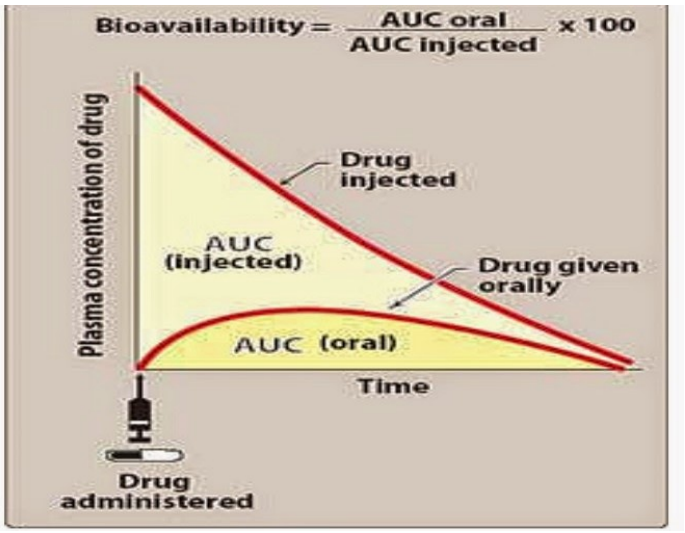
If 100 mg of a drug is administered orally
70 mg of this drug is absorbed unchanged
the bioavailability is 0.7, or 70 ‰ percent.

كمان مرة حابب أذكركم أنه الكتلة للتوضيح و لازم نستعمل التراكيز في الحسابات

Figure

- Bioavailability= AUC oral/AUC IV *100
  *AUC=Area under the curve.
- Larger area is for IV injection, oral area must be less than IV area.
- For the same drug Orel area is smaller or close to IV area. IV peak also is higher than oral peak.
- Curve decline results from distribution, metabolism, Excretion (Every step after absorption).
- Distribution: entry of the drug from the blood to the interstitial fluid

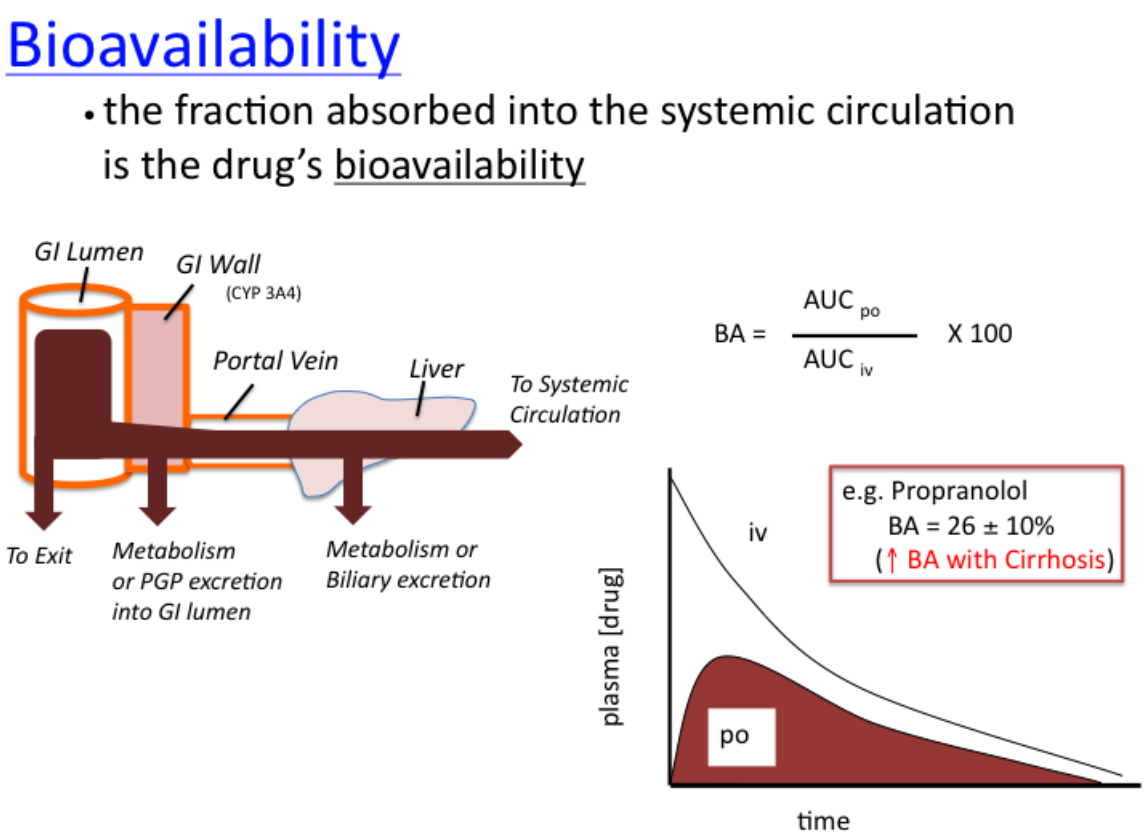
Drug interstitial fluid Enter the cells or rest outside linking to cell receptors (cell surface).
distribution, metabolism, Excretion are over lapped



طبعا لا صوت يعلو فوق صوت ال "أي في" لأنه بالدم مباشره ف كل الكمية بتوصل للدم

- **Figure:**
  bioavailability increase with blood cirrhosis. Low first effect activity.

another figure for it



Factors that influence Bioavailability:

1- First pass metabolism: Intestinal & hepatic biotransformation for oral absorbed drug before reaching general circulation.

Enzymatic reactions, different between individuals, liver diseased patient means low enzymatic activity which will increase the drug bioavailability.

E.g. Propranolol (B-blockers) was written to a patient with liver cirrhosis, the bioavailability for propranolol is 26% (+-10%). The doctor must decrease the dose in order to prevent the probability of overdosing.

الفكرة الي ح أحكيها هون مش مطلوبة بالامتحان بس الدكتور طلب أنه نكون فاهمينها : فكرة ادرينيرجك بيتا بلوكر لازم نكون فاهمينها وعارفينها لأنها مرقت معنا بالفيسيولوجي ف مش غلط لو كنتوا على علم فيها كيف بتكون.

2-Solubility of the drug:

Lipophilic drugs will adhere on the membrane.

Hydrophilic drugs won't cross the membrane.

So, drugs must be large lipophilic (to cross the membrane) with some solubility in aqueous solutions (to move freely in the cytosol) these properties are found in weak acids & weak bases.

3-Chemical instability.

4-Nature of the drug formulation.