Pharmacology

Sheet Slide

number

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- **Bioavailability:**it is the rate and extent to which an administrated drug reaches the systemic circulation.

- **What is the relationship between (first pass metabolisms) and (bioavailability)?**

The drug with an excessive first pass metabolism has a low bioavailability so there is no significant effect of the drug, and the one with low first pass metabolism has a high bioavailability. But the one with no first pass is the best one all of it will reach the blood.

ملاحظة على هذه النقطة: الفرق عند اعطاء مريض 100mg واعطاء الاخر mg200 : بأن ال 200 ملغرام لها أيضا أعراض جانبية كبيرة رغم وصول نسبة قليلة منها الدم لأن الباقي استهلك خلال fist pass effect الا أن الفرق يكون بأن الأعراض الجانبية لا تحدث بعد الوصول للدم انما خلال عملية GI metabolism ويتم تصريفه للكبد فتكون هناك الأعراض الجانبية كتشمع الكبد.

- **Factors that influence/effect bioavailability:**
  - First-pass hepatic metabolism.
  - Solubility of the drug: lipophilicity (penetration of tissue and distribution through cell membranes, water solubility is also important to dissolve in GI system and body fluids (hydrophilicity).

The best level of hydrophilicity and lipophilicity to be largely lipophilic with enough level of hydrophilicity.

Lipophilicity must be high but not excessive because that will affect its solubility in aqueous soln. Also excessive hydrophilicity will affect membranes penetration.

  - Chemical instability: no benefit if the drug degraded in stomach so it should be chemically stable (if it was destroyed during absorption that will affect bioavailability)
  - Nature of the drug formulation: the manufacture and formation of the dosage form.(factors unrelated to chemical properties of the drug, unlike pharmaceutical preparation which deals with the chemical Properties of the drug)

*I can make it in different medicinal forms like tablet or Syrup……

* If we look at the particles size from which we made these preparations, some are fine and others are large

* some additive (inactive gradient) are added to this formulation

<u>All of these affect the rate and the amount of drug that is absorbed:</u>

it will affect the time needed for the drug to be absorbedand also could affect the extent of the drug that will be absorbed. (could be the same drug with same active site but each bind to a different site so both Rate& onset of action will be affected)

ممكن يكون في حواجز لدوا معين بالتالي رح ياثر ..او ممكن هاد الدوا يربط ب بارتكلز معينة بالتالي يزيد فترة بقاؤه في الجسم.

- **Factors influencing the oral bioavailability of drugs :**

- Decomposition in acidic gastric juices.
- Decomposition by hydrolytic gut enzymes
- Degradation by gut microorganisms (the normal, not diseased) and infusion microorganisms effect bioavailability).
- Food in the gut may alter absorption rate and amount (meaning food interaction with drug, if it's insignificant we neglect it, we care just if it is significant).
- Metabolism by gut wall enzymes.
- Metabolism by liver enzymes prior to reaching the systemic circulation.

❖ Bioequivalence and Therapeutic equivalence

Therapeutic equivalence: It is more useful clinically

Bioequivalence: biological equivalence means having the same kinetic profile.

- If drug A and drug B are bioequivalent, can I give A instead of B?

No, because A and B has the same kinetic profile but they differ in dynamic profile, and each may treat different diseases.

Therapeutic: they are similar and comparable. If they are similar in kinetic profile and therapeutic they aren't 100% identical because individual differences between them can't be controlled.

**

Bioequivalence: e.g. When I study drug A and drug B, regardless of rout of administration, dosage form, therapeutic effect…

If they both have the same area under curve, the 2 drugs are bioequivalent.

***Bioequivalence** : Different drugs show comparable bioavailability and they have the same extend and the same rate of absorption.

*Clinically مش ممكن اهتم فيهم

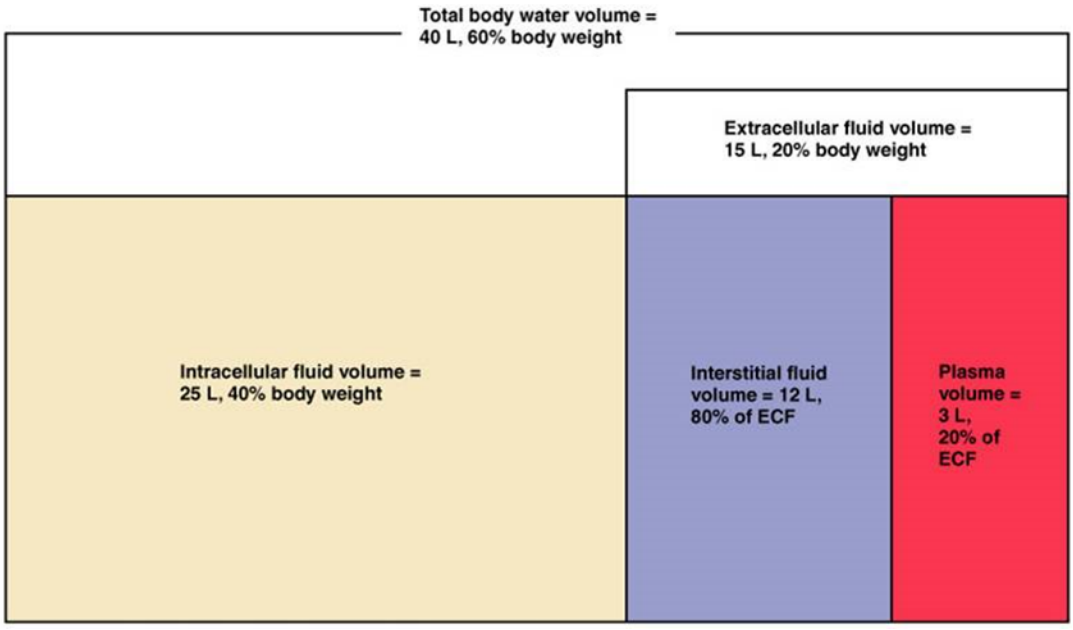
Therapeutic equivalence: 2drugs with same active ingredient, the same amount, same strength, same dose, same rout of administration, same therapeutic response, same onset of action and they are Bioequivalence.

هون زي لما مصنعين يصنعو نفس الدوا ....بصير كل مصنع بدو يضيف ميزات جديدة لهاد الدوا....فبصير متلا اقل سايد ايفكت .... متلا ممكن اغير تغيير معين بالتالي حديت من الديستربيوشن للدوا بالتالي صار سيلكتف اكتر لل سايت اوف اكشن .....هون رح يعطي نفس الريسبونس ...بس الفرق رح يكون السيفتي....فهاد رح يكون احسن

Question: If drug-drug interaction was at the level of absorption did this mean to stop taking one of the drugs?
No, I can give both of them but put separating time between the 2 doses from 6 to 8 to12 hours, one in the morning and the other in the evening.
Or if the Drug-Drug interaction was at the absorption level I can avoid absorption process by giving the drugs IV (directly to the target tissue) instead of oral, so I avoided it by changing the route of administration, for example: antiacids interact with the acid in the stomach to get rid of stomach acidity (neutralize it) but there are many drugs and foods that interact with it at the level of absorption so we used one of the two upper techniques. (note: you should take in consider that if the drug-drug interaction was at the level of distribution or metabolism it will interact the same if taken IV!!!!).

- **DRUG DISTRIBUTION:**

Distribution: transfer of the drug from circulation to different body fluid compartment (reversible process: then will return to the blood in order to be excreted – if didn't, it will accumulate in the body and cause side effects)



This drug will have a transition between these 3 compartments until we reach the equilibrium
*This process depend on concentration
*Equilibrium=same concentration in 3 compartments
Depend on the volume of each compartment
One with larger volume need larger amount of drug.

*This drug which will distributed, will be either free or binded to protein
The free drug will transfer faster than the bindeddrug
لانو لما يكون رابط مع البروتين رح يصير حجمو اكبربالتالي رح يكون صعب انو يتجاوز الحدود البيولوجية..بالتالي رح يقل الديستريبيوشن لالها.

*Distribute the drug from blood to interstitial fluid (fluid btw tissues), then it may inter the cell or it may stay out of the cell but give order through the binding membrane receptors so the effect occurs inside the cells (like if was hydrophilic) .
Note: at the level of membrane mean: the drug stays extracellular binding to receptor, in interstitial but it affects intracellular.
*The largest amount of water is inside the interstitial and intracellular compartments, in blood just 6% water of b.w.

So drug rapidly distribute from blood to tissues→ cause of rapid decline in the curve.

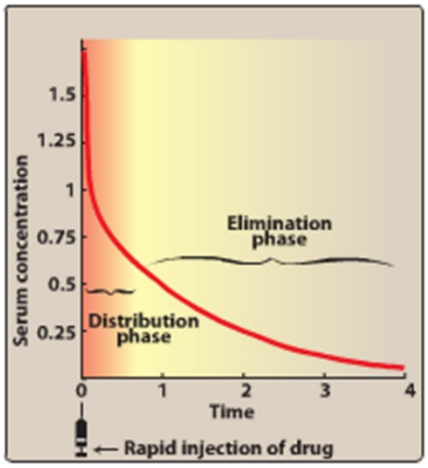


Figure 1.12
Drug concentrations in serum after a single injection of drug. Assume that the drug distributes and is subsequently eliminated.

RAPID Distribution: drug → blood → all the body

SLOWERElimination: drug→ blood → kidney & liver

Elimination mean: slower taken of drug by liver and kidney (just two organs) but distribution taken of drug by cells(the hole body), so distribution is faster than elimination because distribution is for the whole body which act as one unit but elimination of two organs both of them act as two units.

In the curve in the both phases there are both distribution and elimination but in the first part distributionis faster than the other.

❖ Factors affecting drug distribution

1. **Cardiac output and regional blood flow**: cardic output when it is faster the distribution will be fast, so people with heart failure have less distribution. Regional blood mean that the blood has to reach the muscles so if it is slow the distribution will be slow.
   *body organs are 2types: -organs rich of blood flow :liver , heart , intestine, brain , kidney
   -Organs poor of blood flow: skin, some muscles …
   The organs which are rich of blood flow contain large concentration of drug (more distribution).
2. **Capillary permeability:**The brain is rich with blood supply but don't receive large amounts of drug because of barriers.
3. **The tissue volume**. (اللي الو فوليوم اكبر بياخد كمية اكبر).
4. **The degree of binding of the drug to plasma and tissue proteins** (very important)

The attachment of drug to plasma proteins will slower distribution, unlike the drug which attach to tissue proteinsso they have faster distribution (like the affinity of drug to tissue proteins exceeds its affinity to plasma proteins and thus leads to fast and more specified distribution for that tissue.

**Blood proteins:

If the drug was binding to protein the distribution will be lower→the response will belower

هلا لما يكون في دوا المفروض جزء منه يربط ع بروتين .....ونعطيه لمريض وبنفس الفترة ياخد دوا بيفك الارتباط هاد رح يزيد الديستريبوشن بالتالي رح يزيد الريسبونس ....وهاد ممكن يعمل سايد ايفكت....

**Tissue proteins:

*Target: prolongation response……side effect

* Unwanted site: side effect (toxic)

5. **lipophilicity of the drug:**

If the drug will transfer to interstitial fluid it must be hydrophilic

If the drug will transfer into the cell it must be lipophilic

➢ Volume of distribution:

This is the parameter to know in which compartment the drug is (How much tissue volume received the drug).

*plasma proteins binding drug inactive drug**.**

The distribution of the drug is not homogenously because our body is composed of multiple compartments: blood, CNS, stomach, not a one single tissue even each compartment is composed of multiple compartments.

In a beaker the sample is representative: (اي نقطة تركيزها يمثل باقي التراكيز فيه كما الحال في فحص عينة البول أو تنك المي)

unlike our body which is non representative so the volume of distribution is apparent/ hypothetical/not an actual volume it just gives you an idea.

*عشان الدوا يضل ف البلازما لازم يكون حجمو كبير ويرتبط بالبروتينات V>4
*عشان الدوا يضل ف الانترستيشيل لازم يكون صغير ويكون هايدروفيليك 14>V>4
*وعشان يفوت داخل الخلية لازم يكون صغير ويكون هايدروفوبيك

- Vd is useful to compare the distribution of a drug with the volumes of the water compartments in the body.
- Vd is useful for calculating loading dose of a drug

If Vd is big the drug is more diluted than it should be (in the blood plasma), meaning more of it is distributed in tissue (i.e. not in plasma).

شرح لvolume distribution:

قانون الحجم هو:

Volume of distribution=Amount of the drug (كمية حبة الدوا)/concentration in blood

استنتج من القانون: العلاقة بين حجم تدفق الدوا للنسيج عكسية مع تركيزه بالدم

So high volume of distribution the drug: well distributed in tissue (ex: v=12000L the high number is just an indicator)

Low distribution volume mean the drug is less distributed and it still in blood

Volume of distribution تقريبي ويقارب حجم الانسانmean well distributed btw blood and tissue (homologous)

The best state is the well distributed.

*اذا الدوا بيقدر يضل ف موقع محدد ويتخزن فيه فاحنا بنقدر نتحكم ف الساید ایفکت
هلا في بعض الادوية ممكن احدها بالاول بكمية اكبر (loading dose)
هاي الادوية اللي بكون الها ديوريشن طويلة..
فلما اخد كمية كبيرة رح يوصل لاعلى تركيز بشكل اسرع

❖ Half-life: the time needed for the drug to come to its half amount.

**longhalf-life= high effectiveness= high duration of action but low frequency of administration.

- The bigger volume of distribution has longer half-life.

The elimination is slower when the drug is distributed to body tissues because it takes more time to reach the organs of elimination, while if the drug was concentrated in the blood will reach kidney& liver faster and thus eliminated faster.

DRUG CLEARANCE THROUGH METABOLISM

* Elimination causes the plasma concentration of a drug to decrease exponentially.

*لما يزيد الكليرنس رح يقل الhalf time

* كيف بتعامل مع هالاشيclinically?

بزيد الدوز او بزيد الفريكونسي

Clearness mean تنظيف الدم من الدواء

Rout of elimination: -metabolism

-Excretion

Hepatic metabolism through liver called metabolism (الكبد لا يخرج الدواء من الجسم فقط يحوله) but by kidney called excretion.

The drug to be excreted must be metabolized

*metabolism in the liver

* Excretion in the kidney (urine), liver (bile)

من خلال الميتابوليزم رح ازيد البولارتي تبعت الدوا ...ببطل لايبوفيلك....بيقل الريابزوربشن....وبصير الاكسكريشن اسهل

Elimination could be through:

1.1First order elimination

the half life is constant regardless to the dose ….

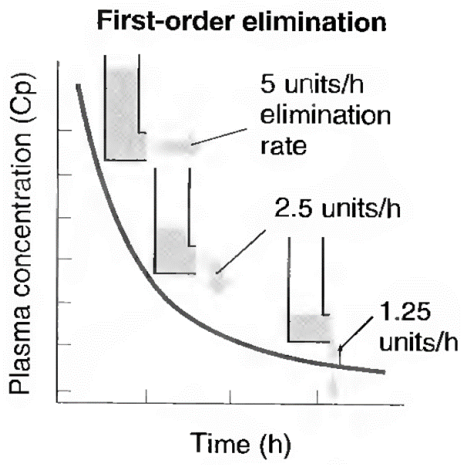
كل وحدة زمن بصير عندي ايليمنيشن لكمية دوا معينة

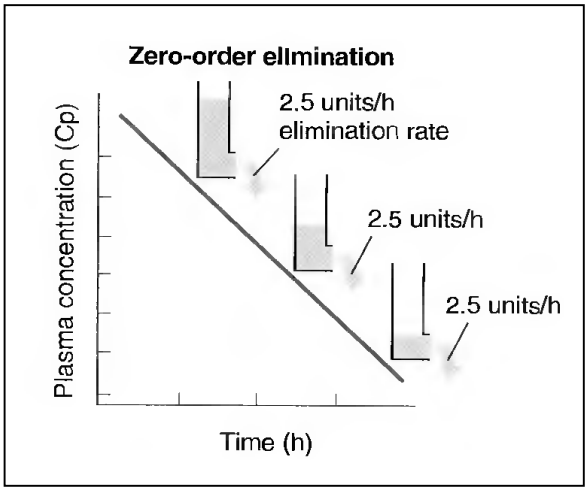
2 .zero order elimination

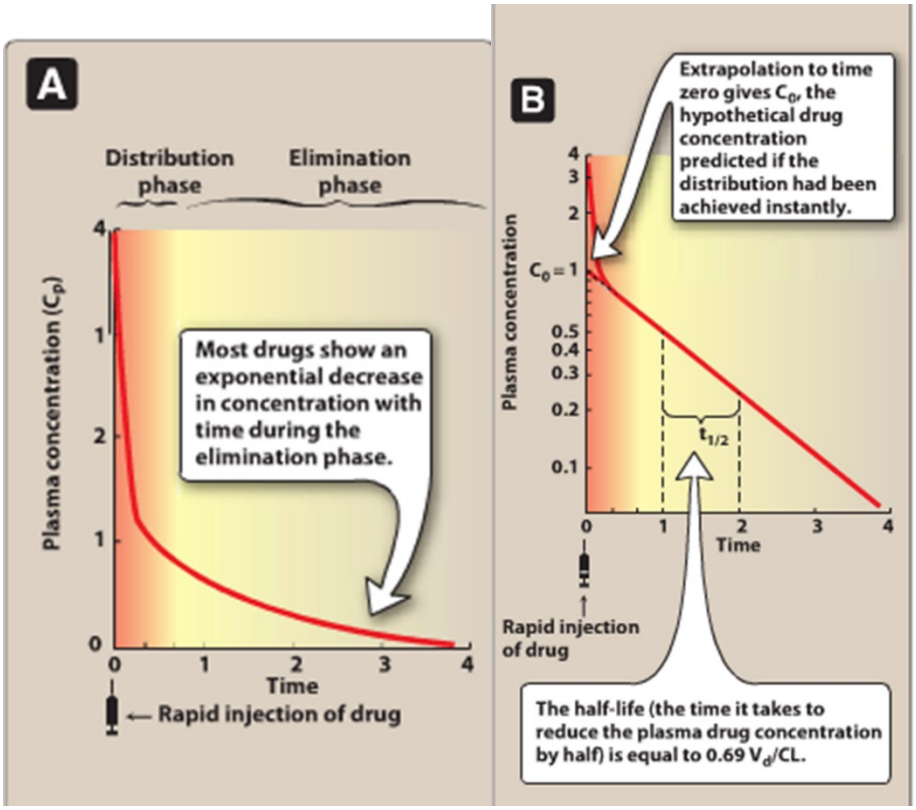
The half life depend on the amount (concentration) of drug in plasma

في بعض الادوية زي الاسبرين في بعض الحالات بتتحول من فيرست ل زيرو ...اذا اعطيتو ب دوز عالية

الادوية اللي بتكون زيرو ...بتدوم لفترة اطول ...لكن اغلب الادوية بتكون فيرست.....


First-order elimination
Plasma concentration (Cp)
5 units/h elimination rate
2.5 units/h
1.25 units/h
Time (h)


Zero-order elimination
Plasma concentration (Cp)
2.5 units/h elimination rate
2.5 units/h
2.5 units/h
Time (h)



*Exponential and linear

First order kinetic:**Exponential** يوجد ثبات بالنسبة ليس في الكمية(fraction constant).Constant decline; constant fraction→ 1oomg-50mg-25mg-12.5mg in half life one hour

نزل عالسريع بالبداية ل 50 ثم بدأ ينزل عالبطيء فهو يقل من ناحية كمية amount لكن ثابت من ناحية fraction

والدواء امن غالبا high level of security and safety

Half life allows the body to get rid of toxicity.

Zero order kinetic; **Linear** is constant in quantity.

100mg-50mg-zero

يكون الدواء خطير جدا- Toxic dose-