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Pharmacology

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Sheet Slides

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Sheet Checklist

Bioequivalence and Therapeutic equivalence.

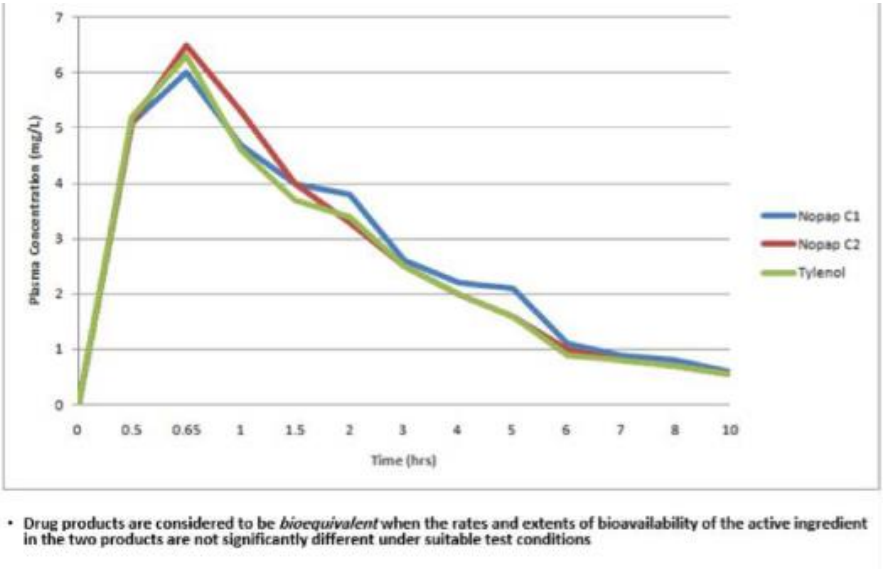
Factors Influencing Absorption.

Revising Bioavailability.

Factors Influencing Bioavailability.

Distribution And The Factors Influencing It, Distribution And Body Water.

Bioequivalence



Bioequivalence is a term in pharmacokinetics used to refer to similarities between drugs in terms of the rates and extents of absorption (they have close to identical bioavailbilities).

We can also compare them their effects (Efficacy, Potency ,Safety ,Therapeutic index, side effects… all dynamics) and if they were similar, we describe them as therauptically equivalent drugs (Recall that we do that in the third phase of clinical trial).

That's all what we need to know about it ☺

Takeaways: What are the characteristics required to call two drugs bioequivalent? What are the characteristics required to call it therapeutically equivalent?

Factors Influencing Absorption (pPBCS – pH, P-GlyP, Blood Flow, Contact, Surface Area)

pH:

Main Idea: Our membranes are permeable for uncharged chemicals more than charged ones, so if we were capable of having the drug in an uncharged form in its administration path, we'll be lucky enough to have more absorption.

Understand the concept and don't dig deep

To understand this idea, we've to go through three concepts

What's pH?

pH is a logarithmic scale used to specify acidity or basicity, the lower the pH the more acidic (less basic) the chemical is and the higher the pH the more basic (less acidic) the chemical is.

What's pKa?

The negative logarithm of Ka, the higher pKa the less acidic the chemical is, and the lower pKa is the more acidic.

You've to know that pKa is a constant value associated with the chemical while pH is dependent on the environment and finally the most important concept that refers to the main idea is about interconnecting these two concepts.

Now, the third concept that interconnects the first two is all about Henderson-Hasselbalch equation

pH = pKa + log (base/acid)

If the base concentration equals the acid concentration, pH=pKa

If the base is present more than the acid, pH > pKa

If the acid is present more than the base, pH < pKa

Now, we'll have to repeat three facts before ending this boring part

Most of our drugs are either weak acids or weak bases.

Stomach environment is highly acidic (low pH), intestines environment is highly basic (high pH).

We absorb the uncharged form of the drug.

So if we had a weak acid (HA) with high pKa in the stomach acidic environment (low pH)

This means according to the equation that it'll stay in the acidic form (protonated) and you can find it logical as the environment is rich in H+, so it'll stay in the uncharged form and get absorbed in the stomach.

While if we found it in the intestines, where the environment is basic and pH is high so according to the equation the basic form (deprotonated) (A-) will be found more and is charged so it'll not be absorbed as well as it was absorbed in the stomach, and this is also logical as the environment is poor in H+.

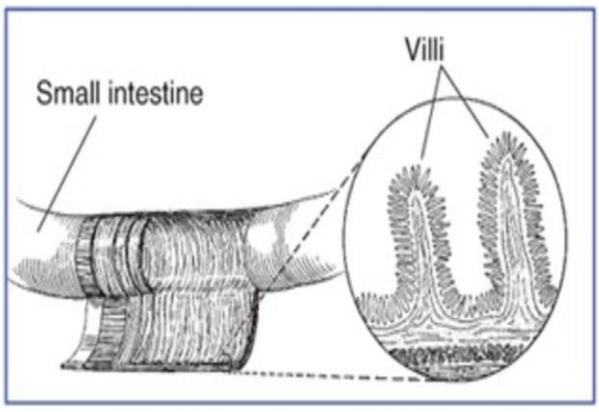
If we had a weak base (BH+) in the intestine's highly basic environment it'll give up its proton (because the environment is more basic and wants it more), this turns it to (B) that is uncharged and gets absorbed, while if it was in the stomach acidic environment that is rich in H+ it'll keep the proton for itself (BH+) is charged and won't get absorbed.

Blood Flow

As we've defined absorbance before that it's about getting the drug into the systemic circulation so blood flow for the region that we're absorbing the drug from is vital.

E.g.: Blood flow for the intestine is more than that for the stomach.

Surface Area



As we've always learnt, the larger our surface area is the more exchange and absorbance take place.

E.g.: With a surface rich in brush borders containing microvilli, the intestine has a surface area about 1000 fold that of the stomach, making absorption of the drug across the intestine more efficient.

Contact Time

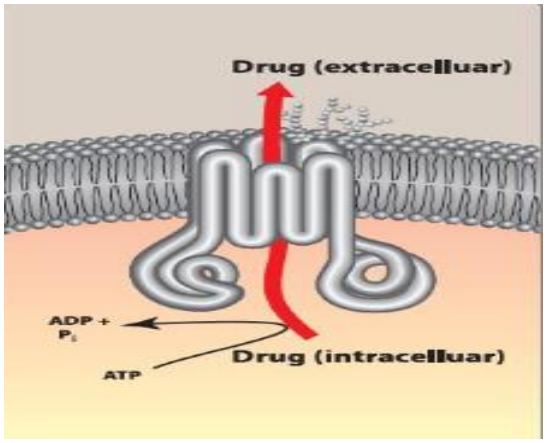
It's logical, as the duration in which we have the drug in a specific region (eg: Intestine) increases the higher the absorbance that will occur. To clear this out, when you have diarrhea the time that the intestine has content in it decreases leading for less contact time.

E.g.: The presence of food in the stomach both dilutes the drug and slows gastric emptying. a drug taken after a meal is generally absorbed more and slowly.

Note: This may be mistaken for the rate of absorbance, what's the rate of absorbance? Amount of drug we absorb for example from the GIT per unit time, now to clear it out contact time is about having the drug there to be absorbed and in cases like diarrhea you'll get it out of your system and no more absorbance will happen. While for the rate of absorbance, we're not interfering with the drug existence in the system, it's about the gradients of diffusion as with time drug plasma concentration will increase and drug GIT concentration decreases as the driving force will decrease by time. Just don't mix them, one is about existence, the other is about what happens when It exists with regards to time.

If not cleared, ask 😑

Expression of P-Glycoprotein



Definition: P-Glycoprotein is a transmembrane transporter responsible for transporting various molecules, including drugs, across cell membranes.

It pumps drugs that enter the cell out of it, that's why this glycoprotein is highly associated with multi drug resistance cases.

Note: Not all drugs, but the ones that are substrates for it.

Found in: Liver, Kidney, Placenta, Intestine, Brain Capillaries, Some microorganisms and in cancer cells.

In areas with high expression of P- Glycoprotein, any substrate drug will have low absorbance.

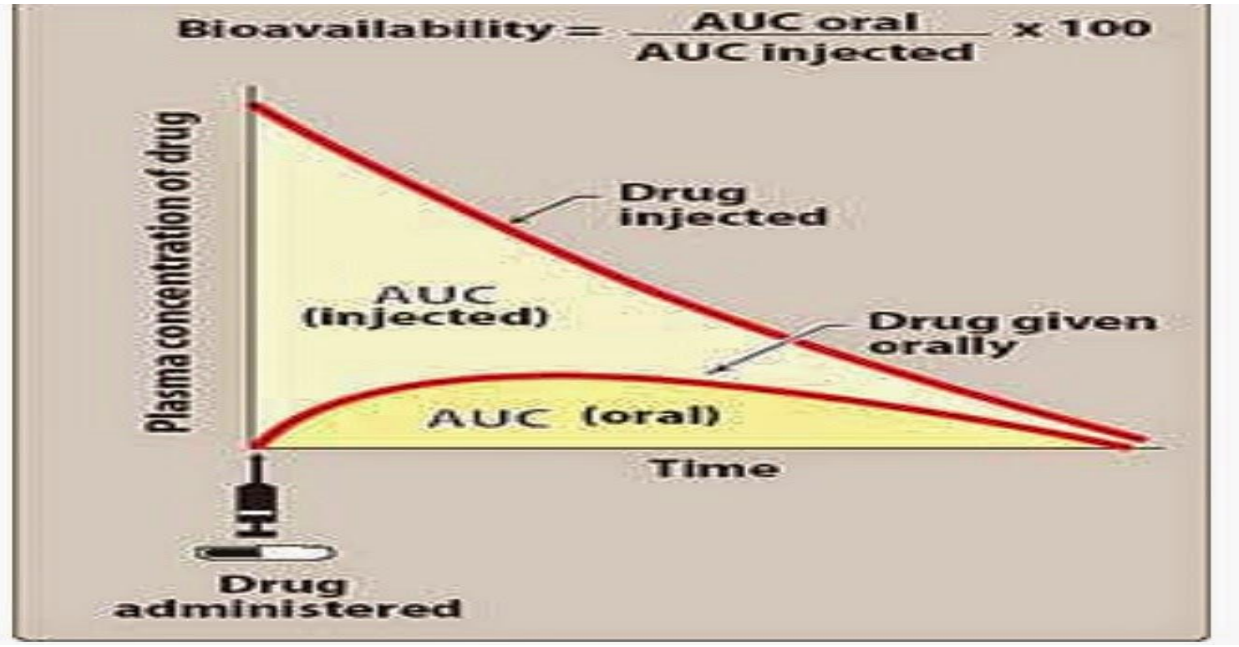
Takeaways: What's absorbance? What are the factors affecting it? Why do weak acids get absorbed in the stomach and why do weak bases do that in the intestine? What is P-Glycoprotein? Where is it expressed? Compare between the stomach and intestine. Try to remember an occasion in which Ali Kilani acted like a P-Glycoprotein.

Bioavailability

Bioavailability is the rate and extent to which an administered drug reaches the systemic circulation.

How can we calculate bioavailability?

Either by the equation we took earlier in which the amount of drug that reaches the systemic circulation is divided by the amount of the dose given.



Or by drawing two curves of drug plasma concentration from two experiments, in one we administer it intravenously and in the other by our studied route of administration.

As we see in the IV curve, it starts at 100% (the peak) then it starts to decline (result of distribution and biotransformation)

While for the oral curve, the curve grows by time as absorbance takes place and the concentration of the drug in the plasma grows then it starts to decline (result of distribution and biotransformation).

Now, we can measure bioavailability by measuring AUC (Area Under Curve) for both curves then by the equation:

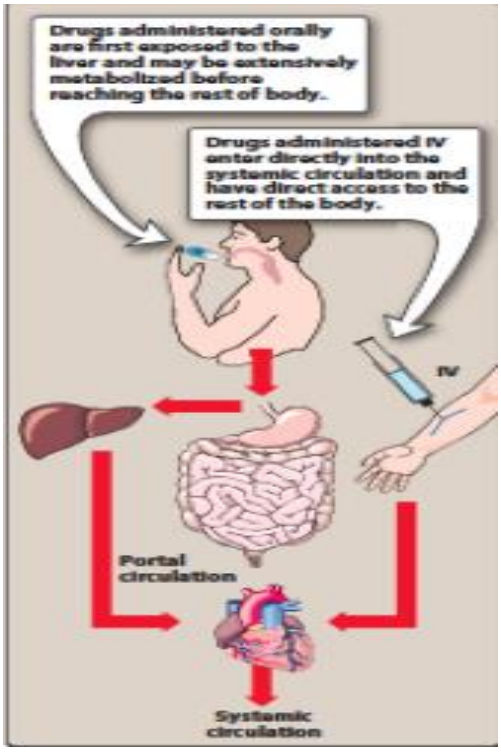
Bioavailability= AUC(orally)/AUC(IV)

Takeaways: How can we measure bioavailability? What's bioavailability?

Factors Influencing Bioavailability (AFSCF, absorbance, first pass effect, solubility, chemical instability, formulation)

Absorbance (we've talked about it)

First Pass Effect



When a drug is absorbed from the GI tract, it enters the portal circulation before entering the systemic circulation. If the drug is rapidly metabolized in the liver or gut wall during this initial passage, the amount of unchanged drug entering the systemic circulation is decreased, this affects the efficiency of many orally taken drugs.

Most routes of administration avoid it except for the oral path and in certain limits the rectal path (suppositories).

E.g.: More than 90% of the absorbed nitroglycerin is cleared due to first pass metabolism, so we must consider many things when we determine the dose like:

- Amount absorbed (measured by fraction of absorbance (bioavailability)).
- Amount metabolized due to first pass metabolism (measured by the extraction ratio of the liver (also known as liver clearance rate) and it depends on the blood flow to the liver and the metabolic rate of the drug).
- Therapeutic index and window
- The case and the amount of effect we want to get
- Protein binding (will be discussed later in the sheet)
- Other kinetics

All of these factors are important, so we exceed the minimum effective concentration, if we don't then we won't have an effect.

Solubility of the drug.

We know that for a drug to pass through the membrane passively it has to be lipophilic but we'd take into account that our compartments (ICF, ECF (Intravascular, Interstitial)) are aqueues.

So the ideal drug must be lipophilic, yet have some solubility in aqueous solutions, that's why our drugs are weak acids/bases (can exist in lipophilic and hydrophilic states)

This is measured for by lipid water partition coefficient (Lipophilicity and solubility in aqueous solutions).

Chemical Instability

Some drugs, such as penicillin G, are unstable in the pH of the gastric content (acid labile).

Insulin and other peptides and proteins get destroyed in the GIT by proteases and degrading enzymes.

Nature of drug formulation

This has nothing to do with the chemical and physical properties of the drug, it's about its formulation and configuration that can affect solubility and dissolution, therefore affecting absorbance and bioavailability.

E.g.: Particle size (affects solubility in suspensions), presence of excipients (such as binders and dispersing agents, a paracetamol pill isn't 100% paracetamol), crystal polymorphism (D and R, Stereoisomerism), salt form, enteric coating (some drugs have coatings (mostly capsules) that protect it from the acidity of stomach, the coating is also subjected to dissolve in a basic environment (intestines) leading for the release of the drug.

> Takeaways: Discuss the factors affecting bioavailability, what do you know about the first pass effect? What routes face it? How can we measure for it? Discuss solubility and chemical instability.

Distribution

Now, we've covered absorbance and we have the drug in our systemic circulation, it's time to distribute it in our compartments.

There are multiple factors that affect distribution

Factors That Affect Distribution: (POBCpT: Protein Binding , Organ specificity, Blood flow- tissue mass ratio, Capillary permeability , pH, Transport Mechanism)

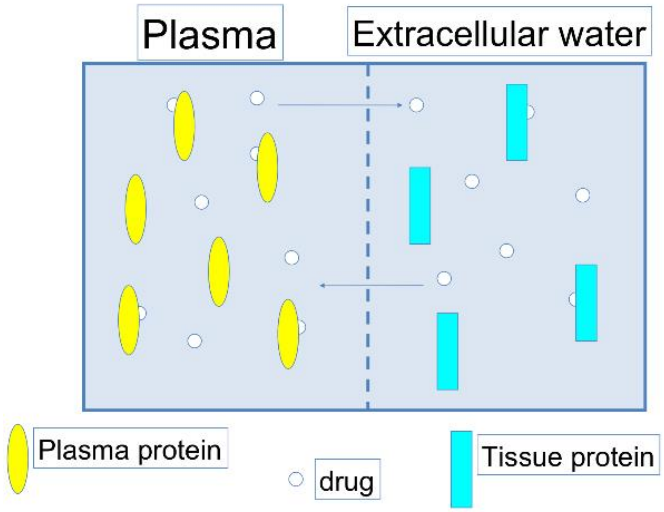
Protein Binding

As the drug enters the blood circulation, it'll face plasma proteins (albumins and globulins).

Some drugs have high affinity for these proteins, so they bind to them forming a drug-protein complex that can't be transferred out of the Intravascular space unlike the unbound free form that will be capable of getting out of it (so we conclude that the free form is the biologically active form).

Because of plasma proteins high binding capacity to various chemicals, the binding is described as nonspecific (Recall from sheet 5 that specificity is about having preference for a substance rather than others, but this is not the case here, the binding site was made for something else (endogenous) and it happened that our drug has affinity for it (To understand more, think of Bilirubin-Aspirin example in Biochemistry).

This binding depends on the affinity, dissasociation constant, protein's binding capacity (number of binding sites available) and drug concentration.



For these drugs, we'll have an equillibrium between the bound (inactive) and free form (active), as free ones get distributed and leave the Intravascular space, the equillibrium will shift and bounds will get freed and so on, so we can see that protein binding led for:

1- Reducing the intensity of the action (If all were free at the same moment, the effect would be powerful)

2- Prolonging the duration of the effect (frees leave and act, bounds unbound).

Protein binding can also cause drug-drug interaction, it happens when we have two drugs with affinity for the same spot on a plasma protein, they'll compete to bind to it. This competition increases the concentration of the free form of the drugs leading to an intense effect that isn't wanted (especially if it reaches the toxic levels).

E.g.: The anticoagulant Warfarin and the anti-inflammatory drug Phenylbutazone do have the same binding site, so they compete, and the free concentrations increase leading to the intense effect (bleeding because of Warfarin increment).

Capillaries Permeability

Drug size and solubility in addition to the presence of barriers and number of tight junctions, all affect permeability.

For instance, the brain, prostate and the eye are difficult to penetrate because of the presence of huge amounts of tight junctions between endothelial cells.

On the other hand, lymphatic vessels and the liver have high permeabilities.

Blood Flow-Tissue Mass Ratio (Perfusion Rate)

Perfusion rate: the rate of blood flow through the capillaries per unit mass of the tissue.

Some organs like the kidney and liver have high perfusion rate, while others like the skin and bones have low ones.

Organ or Tissue Specificity

Some drugs like to accumulate in the adipose tissue or synovial fluid for example.

Another example, as for bones we said that they have low perfusion rate as a result whenever we're designing a drug that targets bone tissue we make sure that its features and characteristics have tendency toward our bones more than other tissues, so we compensate for the low perfusion rate.

Regional differences and pH

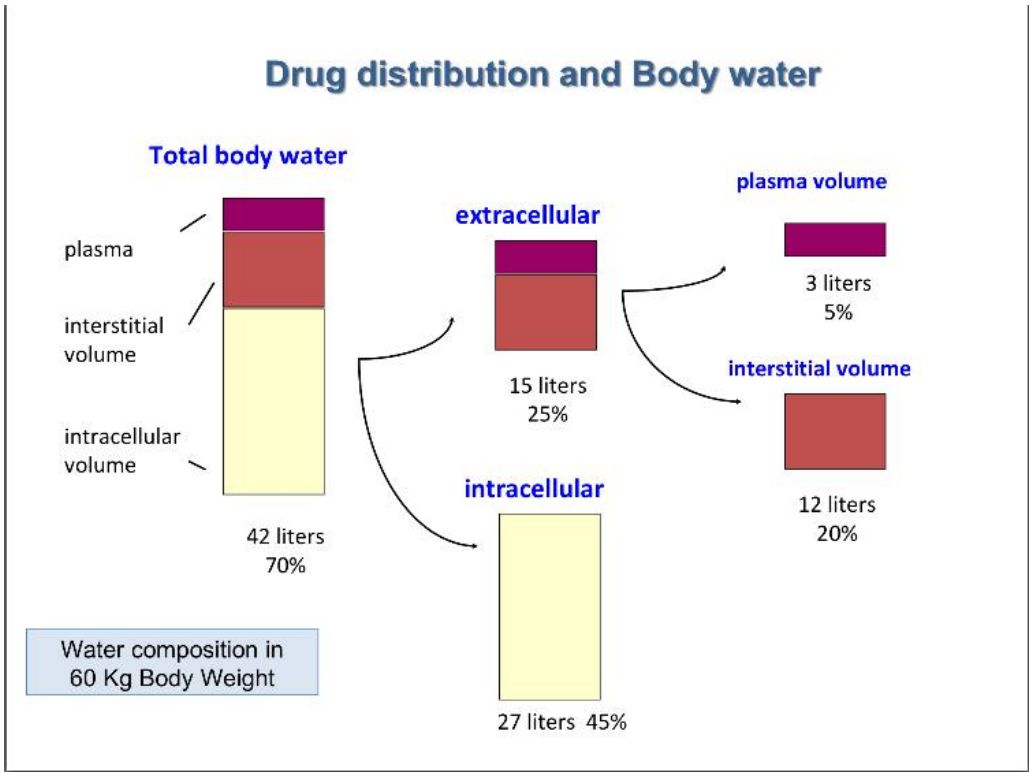
As we have said in the factors affecting absorbance, here it'll also affect distribution and movement between compartments.

E.g.: If you were told that an inflamed area has low pH, you'll give your patient a weak acid anti-inflammatory drug.

Transport Mechanisms Available

Revise Sheet 7 and add to your knowledge that it's not just entrance but also about pumping out through P-Glycoprotein.

Drug Distribution and Body Water



As we see in the figure 70% of our body is water, 45% of our body is water in the ICF, 25% of our body is water in the ECF (5% Plasma, 20% Interstitial).

So what properties govern the compartments that the drug can get to?

Solubility And Size

A drug can be in the:

Intravascular compartment only, if it's large and hydrophilic and it makes sense as it'll be soluble in the hosting environment and large enough to not pass through the

endothelial junctions, so it's only in 3L of the 42L of the 60kg assumed individual in the figure.

E.g.: Heparin

Extracellular compartment only (Intravascular and Interstitial) if it's small and hydrophilic as both environments are aqueues and its small size allows it to pass through the endothelial junctions, so it's only in 15L of the 42L of the 60kg assumed individual in the figure.

E.g.: aminoglycosides.

Note: we're viewing the general concept, but if we had advanced mechanisms we can transport it into the intracellular fluid.

Total body water if it has low molecular weight and is hydrophobic, it'll move through the endothelial junctions or even through endothelial cells membranes and it'll pass the membranes of the cells in the peripheral tissue.

Note: Some drugs have high binding affinity for specific tissues (e.g. the fatty tissue) so they accumulate there, and the circulating drug concentration decreases therefore affecting the equillibrium between free circulating drug and distributed drug in the different tissues.

Takeaways: Define distribution, what are the factors affecting it? Discuss drug-drug interactions, discuss drug distribution in body water.