SHEET NO.

PHARMACOLOGY

DOCTOR 2019 | MEDICINE | JU

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Quick revision

- Last time we talked about Routes of administration , in which the oral route is the most variable and complicated one, one source of variability is drug absorption which depends on transporters (the genetic variation between individuals lead to differences in transporters and thus variations in the absorption process)

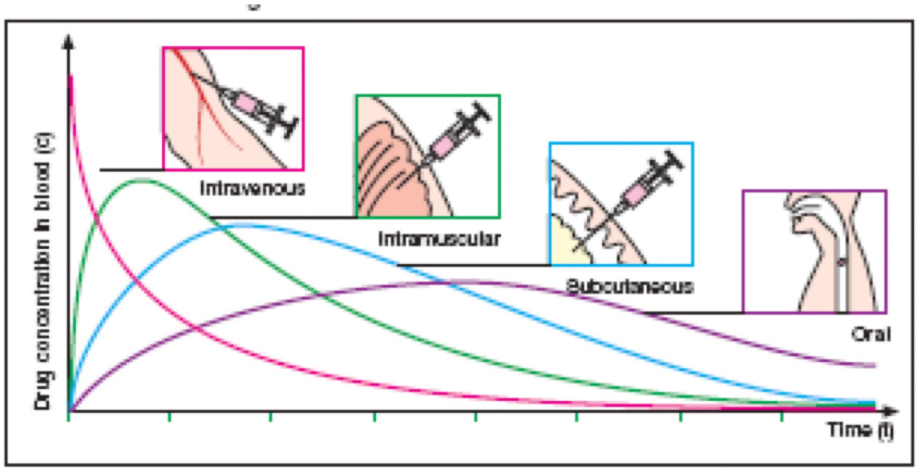
- patients may have diseases such as stomach and intestinal diseases what leads to absorption variability too.

- We sometimes go through sublingual administration for faster effect (than oral)
- we go through rectal route-mostly with kids and unconscious patients.

- We have also mentioned injections and its advantages and disadvantages (injections are faster than oral route) its rapidity causes peak .

Routes of drug administration

• Now we're going to see a graph which shows routes of drug administration in terms of levels of concentration of drug in patient's blood within time.
• (X-axis: time, Y-axis: drug conc. In the blood)



B. Mode of application and time course of drug concentration

• The pink curve shows the Intravenous injection method, in which we inject the drug directly in the blood, the highest level of drug concentration that can be achieved in the bloodstream is by using this route.
- The fastest route of drug administration is the intravenous injection, it gives the maximum conc. of drug in the blood within seconds. However, by doing this, we expose the receptors to high amounts of the drug, and we get a higher chance of adverse and side effects to happen.
• the curve in purple represents the oral route of administration, As the absorption is low and the drug concentration in the blood is less compared to intravenous injection,therefore, both the therapeutic effects and side effects are less.

- That's why there are drugs that cannot be injected intravenously, and are taken orally, for example, so that they get absorbed slowly, with a low (almost non- existing) peak of concentration and therefore, we avoid exposing the receptors to high amounts of these drugs, so we decrease the chance of side effects to happe

• The green curve represents the Intramuscular injection, in which the drug is injected directly into the muscles, drug's level of concentration Builds a peak after a short while, but it is relatively less than the concentration Level built after intravenous injection.

• The blue curve representing the subcutaneous injection builds a lower peak after a longer while. While the lowest peak is caused by oral administration of the drug (purple curve).

Drug absorption

• Is the rate at which a drug leaves the site of administration and the extent to which this occurs.
• the Physical factors influencing absorption are :

A. Blood flow to the absorption site:
- intestine absorption is more favorable over that from the stomach because the blood flow to the intestine is much greater than the flow to the stomach.

B. Total surface area available for absorption:
-Small intestine is the principal region of absorption of orally administered drugs, because the intestine has a surface rich in microvilli.

C. Contact time at the absorption surface:
-The rate of transit through the stomach and intestine is an obvious rate limiting factor in absorption. For example, if a drug moves through the GI tract very quickly, as in severe diarrhea, it is not well absorbed.
- Elderly, however, have chronic constipation, and drugs move slowly in the GI tract,thus, giving them more absorption.

Bioavailability

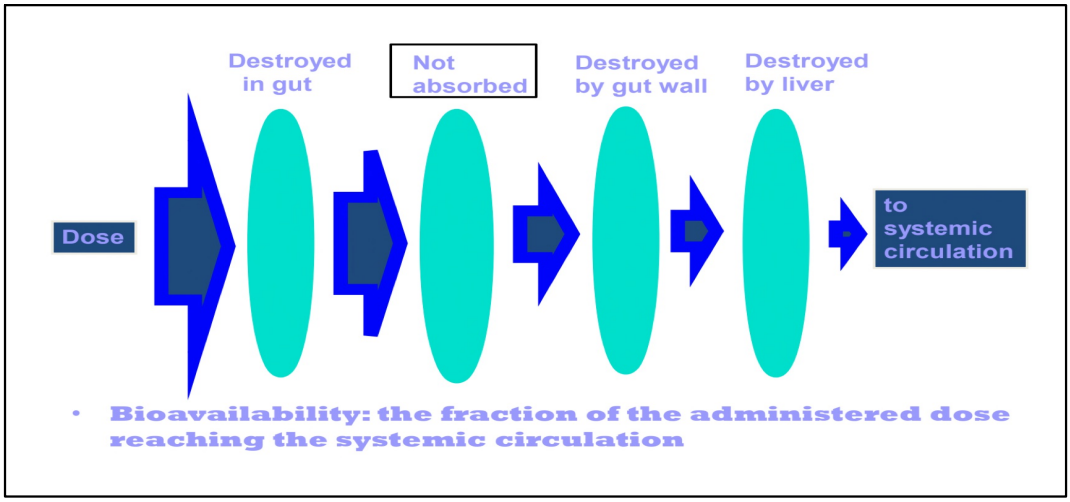
• Is the fraction of administered drugs that reaches the systemic Circulation.

-When a drug is taken orally, for example, it travels through the stomach and duodenum, and a fraction of it gets destroyed there. Another fraction of it gets metabolized in the liver as well. The remaining fraction of the given dose that reaches the blood circulation is then measured and called the Bioavailability.

• Expressed as the fraction of the administered drug that gain access to the systemic circulation.
- For example if 100 mg of a drug administered orally and 70 mg are absorbed unchanged, the bioavailability is 70%.
• Factors that influence bioavailability:

1-first-pass hepatic metabolism

-Drugs are first carried in the portal circulation to the liver where they may be metabolized.
- Loss of drug by this passage through the liver is termed THE FIRST-PASS EFFECT.
-This can be very significant and may result in virtually complete elimination of the original drug.

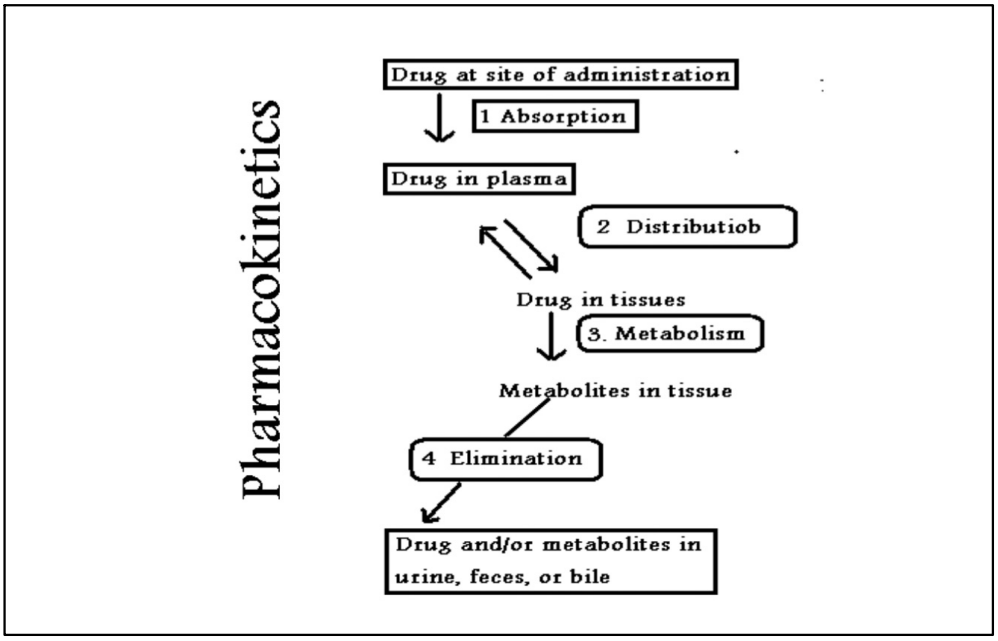


Note

- there is an amount of the drug that is not absorbed due to its expulsion by p-gp.
- In the gut, there are enzymes that destroy the drug, so first pass metabolism starts there, and we lose a fraction of the given dose.
- To calculate Bioavailability, we divide the remaining amount of drug that reached the blood circulation (after the last arrow) over the full administered dose (the first arrow).

2. solubility of the drug:

Very hydrophilic drugs are poorly absorbed, because of their inability to cross the lipid rich membrane.



Distribution

• Once the drug enters the body, it distribute into one of three functional compartments:

A. Plasma

• if the drug has very a large molecular weight or binds extensively to plasma proteins. So the drug is effectively trapped with the plasma (vascular) compartment.

- These drugs with large molecular weight could be small ones that were administered orally and attached to albumin after diffusing through the wall of intestines, and they could be large molecules taken orally and passed the wall of intestines either with small amounts or by transporters, and they could be large molecules that weren't taken orally.
- 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.

B. Extracellular fluid

- if the drug has low molecular weight but it is hydrophilic, it can move through the endothelial junctions but cannot cross the membrane to inter the cells. So they will distribute into both the plasma and the extracellular fluid compartments.
- 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 4L of plasma + 10L of ECF)

C. Total body water (plasma+ ECF +ICF)

- if the drug has low molecular weight and hydrophobic, here it moves through the membranes into the cells.
- it will distribute into a volume of about 60% of the body weight (42 L in a 70 kg individual).

Notes

- Some drugs, lipid soluble ones, are stored in the fatty tissue in an equilibrium with free circulating drug

- A fraction of the dose of these lipid soluble drugs is stored in fatty tissues after administration, so these tissues act as a reservoir of these drugs, and equilibrium between the reserved portion and the free circulating portion is maintained, although this equilibrium is not static, because a portion of the circulating drug will be eliminated by the kidney then excreted, and another portion will be metabolized in the liver.

- To compensate the lack of the drug in the bloodstream, the equilibrium is shifted, and fatty tissues release a portion of the reserved drug, and so on to maintain this dynamic equilibrium>>This prolongs both the effect and the half-life of this drug.

- An example is azithromycin which is currently tried against corona virus, when it is administered for a period of 5 days, it takes more than 15 days for the body to consume it completely.

- Some areas of the body (e.g. the brain, the placenta) are not accessible to drugs due to anatomic barriers (the blood brain barrier, and the structural closure of placenta) and that is why we exclude the brain and placenta when talking about the volume of distribution of drugs.
- 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

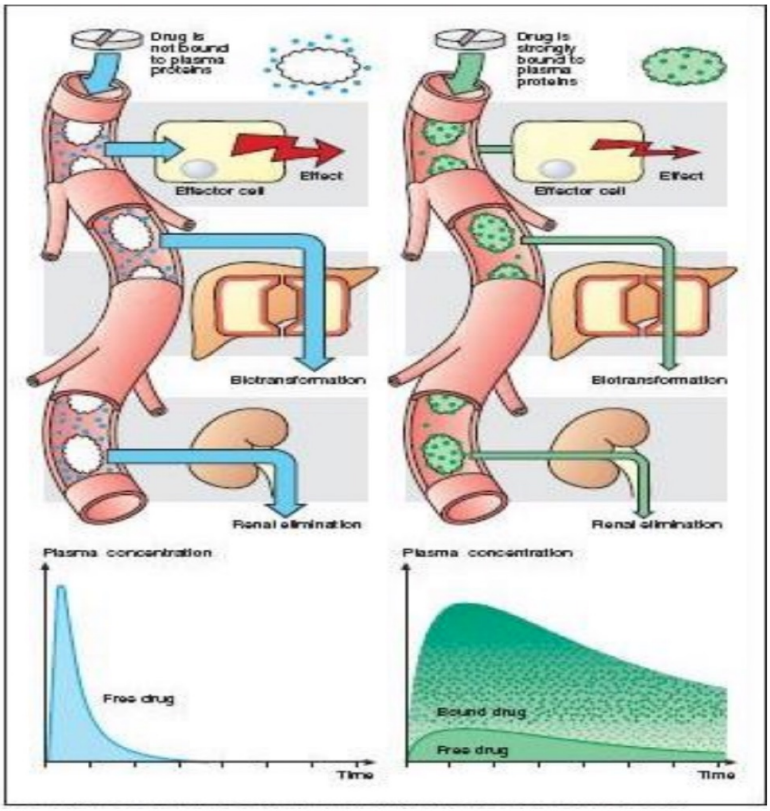
Drug binding to plasma albumin

• 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 (because the effect of the drug depends mainly on its 3D shape, and when it binds to a plasma protein the 3D shape changes, so bound drugs cannot exert their intended effect, only free ones can).

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

• This type of agents have a high affinity for albumen and are not bound to any significant extent by other constituents of the tissues.

• The equilibrium that happens here is like the one before, it is not static, when the free drug decreases in the bloodstream due to metabolism or elimination, a portion of the bound drug is released and so on , and we can say that the plasma proteins act as a reservoir of these drugs.



• This first picture here shows what happens to a drug that is not bound to plasma proteins, a fraction of it exerts the intended biological effect, while the rest of it gets either metabolized in the liver or eliminated in the kidney.
- The concentration of this drug is high in the bloodstream, but the duration of its action is short.

• This 2nd picture here shows what happens to a drug that is strongly bound to a plasma protein,when this drug enters the bloodsream, a fraction of it gets bound to plasma proteins, while the rest remains free and either exerts its intended biological effect or gets destroyed in the liver and kidney in a way that maintains equilibrium as we discussed before.
- The conc. of this drug in the bloodstream is lower than the drug in the other drawing, but the duration of its action is much longer.

• Binding is reversible and is dominated by electrostatic, hydrogen bonding and hydrophobic interactions.
• There are several binding sites on albumen. Lipophilic drugs are strongly bound.

Drug interactions

• Drug interactions occur on albumen by the displacement of one drug by another. Can raise dose of some drugs to toxic levels.
- For example, if drug A and drug B were strongly bound to plasma albumin, when taking these two drugs at the same time, they will compete over binding albumin, and the amount of bound drug A will be less than when it is administered alone, same thing with drug B, leading to more free drug molecules, and higher chance of getting adverse and side effects.
• For example Anticoagulants (Warfarin) can be displaced by the anti- inflammatory agents Phenylbutazone.
- Warfarin is used to prevent blood clotting, when it is displaced, more free Warfarin will circulate in the blood, liquefying it, this could cause internal bleeding.
- Warfarin is one of the narrow therapeutic index drugs, so increasing the level within the blood of your patient means toxicity.

Pharmokinetics 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 Less body water, less muscles, less volume of distribution, more fat.

• Water soluble drugs (in plasma and ECF): lithium,aminoglycosides, alcohol, digoxin
- Serum levels may go up due to decreased volume of distribution
- Because body water is less, concentration of drug within blood is higher, which leads to toxicity.
- When prescribing a drug with narrow therapeutic index to a geriatric patient, we must lower the dose sometimes, we cannot give a 70-year-old patient the same dose we usually give to a 40-year-old one.

• Fat soluble drugs: diazepam, thiopental, trazadone
- Half-life increased with increase in body fat.

- Having more fat in their bodies provides reservoir to the drug, larger portion of the drug will be stored in fat tissues, concentration of drug won't really change, the amount of it will be less, but with less body water, the concentration almost doesn't change.
-The concentration of the reserved drug will increase; thus, the drug's half-life increases, So when the drug is administered for the first time, a fraction of it will remain in the fatty tissues, and when the second dose is given to the patient, there will be already existing drug in their bloodstream (taken from the fatty tissue) and in their fatty tissues, too.
-In addition to the drug that is given on the second dose, this will lead to accumulation of the drug within the patient's blood; thus, equilibrium will be shifted towards the metabolism and elimination of the drug.
- When prescribing such drug to a geriatric(Old) patient we should lower the dose and monitor the patient to prevent accumulation of it.

Pediatric Distribution

• Body Composition, in pediatrics:
- increase in total body water & extracellularfluid
- decrease in adipose tissue & skeletalmuscle

• These differences in body composition are due to the presence of growth hormone in big amounts in children, it becomes neglectable at the age of 18-21.

• Protein Binding:
- High levels of albumin, bilirubin, 1-acid glycoprotein
- High level of bilirubin causes jaundice (hyperbilirubinemia) it usually isn't pathological though, it is only physiological, exposing the baby to enough sunlight helps in healing them.
• Tissue Binding:
- compositional changes, (not fully developed tissues)

Metabolism

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

• 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
• Because these drugs are excreted via the urinary tract (as urine), so they need to be more polar
-Conjugation = linking these drugs to other compounds to make them polar/hydrophilic.
• Metabolism often, but not always, results in inactivation of the compounds.
• Some drugs are activated by metabolism, these substance called prodrugs.

• Phase I metabolism

• Drug metabolism occurs in two phases:
• Phase I reactions function (e.g., oxidation, reduction, hydrolysis) alter chemical reactivity and increase water solubility.
• Phase I reaction frequently catalysis by the cytochrome P450 system (also called microsomal mixed function oxidase).

Drug + O2 + NADPH + H+ → Drug modified + H2O + NADP+

• To date, more than 50 unique isoforms of this enzymatic system (CYP2D6, CYP3A4) have been identified to play a role in human drug metabolism.

• phase II metabolism

• If the metabolite from phase I is polar enough, it will be excreted by the kidney, But if it is still lipophilic, it is to be retained in the kidney, a subsequence 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.
• The resulting compounds are usually of high molecular weight (less soluble); thus they are excreted via the GI tract (feces) instead of the urinary tract (urine).

CYP family of enzymes

• Found in liver, small intestine, lungs, kidneys, placenta
• Consists of > 50 isoforms
• Major source of catalytic activity for drug oxidation
• It's been estimated that 90% or more of human drug oxidation can be attributed to 6 main enzymes:
• CYP1A2
• CYP2C9
• CYP2C19
• CYP2D6
• CYP2E1
• CYP3A4
•In different people and different populations, activity of CYP oxidases differs.

Cytochrome p450 system

• 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, Rifambin significantly decreases the plasma concentration of HIV protease inhibitors.

• Cytochrome enzymes inhibitors, omeprazole 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.

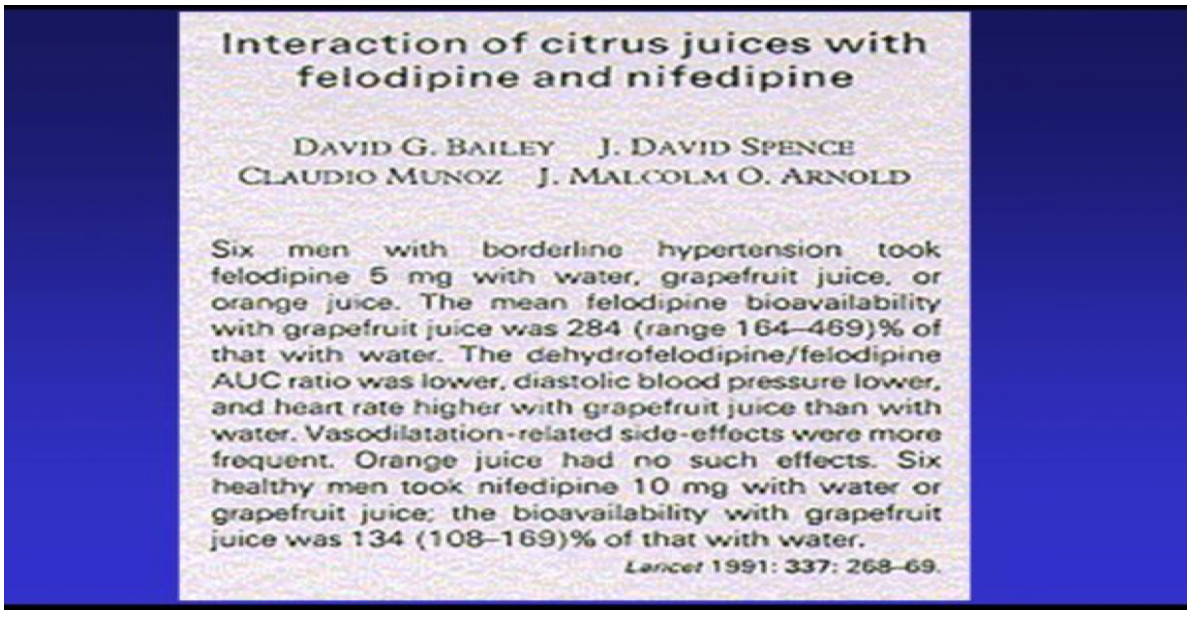
- more explanation for fase I and fase II metabolism

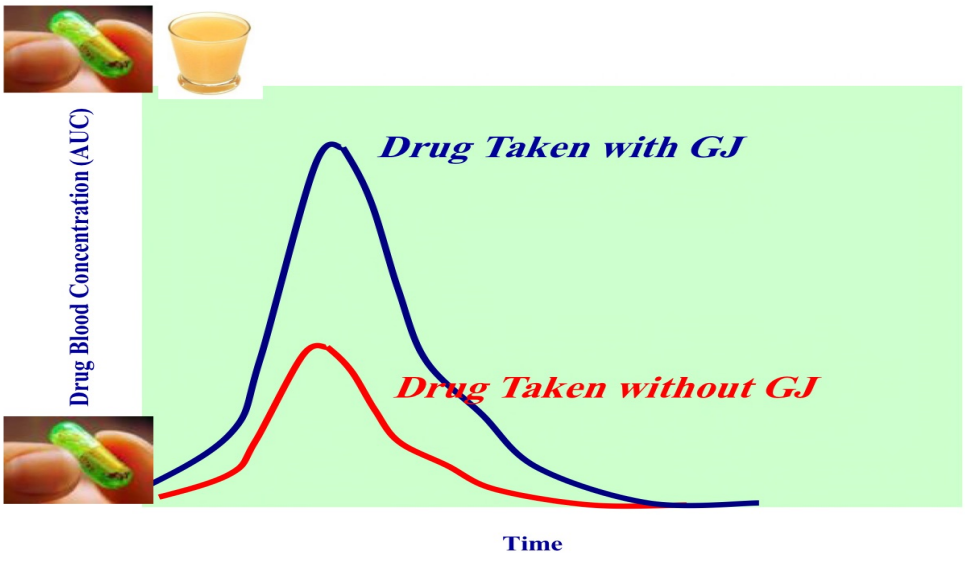
- The kidney cannot efficiently eliminate lipophilic drugs that readily cross cell membranes and are reabsorbed in the distal convoluted tubules. Therefore, lipid-soluble agents are first metabolized into more polar (hydrophilic) substances in the liver via two general sets of reactions, called phase I and phase II.
- The lever starts metabolizing the drug in the first phase, by oxidation/ reduction/ hydrolysis, to alter the chemical reactivity and increase water solubility.
- If the resulting drug is polar/ hydrophilic enough, it gets eliminated with urine.
- If not, it goes to the second phase of metabolism, the conjugation phase, in which it gets linked (conjugated) to an endogenous substance, like glucuronic acid.
- Now the conjugated molecule is usually big in size, so it gets out of the body via the GI tract in feces instead of urine.
- The enzyme family that catalyzes these metabolic reactions is the CYP family.

- more explanation for drug-drug interactions in the CYP enzymes

- The CYP enzymes are a target of drug-drug interactions, and they could be induced by inducers and inhibited by inhibitors.
-Let's keep in mind that these enzymes function in metabolizing drugs, so when they get induced, more drug is metabolized and then eliminated (less concentration of the drug in plasma). And when they get inhibited, less drug is metabolized (more concentration Of the drug in plasma).
More drug in plasma= increased Bioavailability

- Now we get to the examples, a certain CYP enzyme is responsible for metabolizing HIV protease inhibitors, and this enzyme is induced by Rifampin, so when Rifampin induces this enzyme, more of HIV protease inhibitors are metabolized and eliminated, so the conc. of HIV protease inhibitors in the plasma decreases.
-That's why we say that Rifampin decreases the plasma concentration of HIV protease inhibitors.
- Another example, we have three CYP enzyme isoforms that metabolize warfarin , these enzymes are inhibited by Omeprazole , so it inhibits their activity, and less Warfarin is metabolized and eliminated, so the concentration of Warfarin in plasma elevates (increases
- We previously said that Warfarin liquefies blood to prevent clotting, but high concentration of it in the plasma inhibits coagulation, leading to serious bleeding.





Some drugs influenced by grapefruit juice

Drug	AUC increase
felodipine	~ 3 fold
cisapride	~ 1.4 fold
cyclosporine	~ 1.5 fold
saquinavir	~ 2 fold
terfenadine	~ 2.5 fold
buspirone	~ 9 fold
lovastatin/simvastatin	~ 10 fold

-What we need to know is that grapefruit juice increases the conc. In plasma for some drugs.
*Cyclosporine was discussed earlier this course as a narrow therapeutic window drug, so increasing the conc. of it by 1.5 folds will make it toxic.

CYP isoforms vary with age

• For example, clearance of midazolam by CYP 3A4 and 3A5 goes from 1.2 ml/min/kg to 9 ml/min/kg over first few months of life.

- Therefore, the hardest age range to prescribe drugs to is1 day – 6 months old, because these enzymes are unsteady.
• Carbamezapine (3A4) clearance faster in children than adults – requires higher doses.

Thank you..