Computer Aided Drug Design
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Lecture - 10
Drug - ADME

Hello everyone, welcome to the course on computer aided drug design. We will continue on the topic of ADME, absorption, distribution, metabolism and excretion. We will look at lipid solubility.

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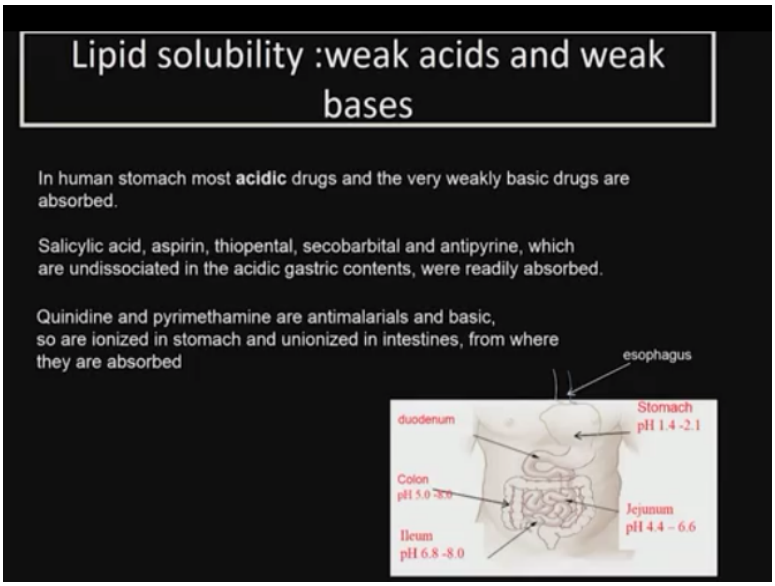

How drugs which are weakly acidic or weakly basic, how they dissolve in various parts of the stomach, small and large intestine. For example, like I have been telling that there is a lot of difference in the pH. If you look at pH of the stomach, it is about 1.4 to 2.1. If you go to duodenum pH changes a little bit, and then jejunum pH is 4.4 to 6.6, ileum it is 6.8 to 8, colon 5 to 8, so extremely acidic going right up to basic.

So the drugs depending upon the whether it is weakly acidic or weakly basic, they will start dissociating depending upon the pH and so the absorption of the drugs may change dramatically. Some drugs may get absorbed in the stomach, some drugs get absorbed down the line into the small intestine because of the differences in pH. So we look at that. In human stomach, most acidic drugs and the very weakly basic drugs are absorbed.

So that is in the stomach, so highly acidic drugs and weakly basic drugs. Salicylic acid, aspirin, thiopental, secobarbital and antipyrine, which are undissociated in the acidic gastric contents, because they are acidic drugs and pH is also highly acidic, so they do not get dissociated, so they get absorbed. So aspirin that is why it acts very fast. So if you want to have very fast-acting drug, make it acidic or very little basic, so that it will get absorbed in the stomach.

Quinidine, pyrimethamine, anti-malarials and basic they are ionized in the stomach, because you have acidic, whereas they are unionized in the intestine, so they get absorbed. So if the drug gets ionized depending upon the pH it becomes very polar. So it cannot cross the lipid barrier, because lipid barrier it is very hydrophobic; that is the strategy. So if you want a quick acting drug, you try to make it highly acidic or weekly basic.

If you want to have a very slow acting drug, then if they are very basic and they will go down the line maybe they will get absorbed in the small intestine. So let us look at the pKa, pKb, which talks about the dissociation constants of a weak acids, weak basic and so on

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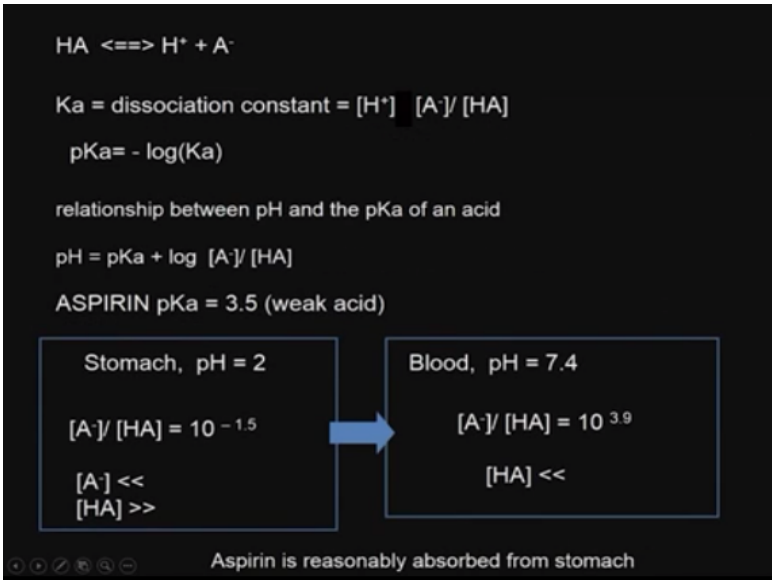

Let us look at it. Suppose you have HA it dissociates as H+ and A-, so the dissociation constant is a H+ * A-/HA, given like this pKa, is nothing but log(Ka), dissociation constant is pKa is given as - of logarithm of Ka. There is a relationship between pH and the pKa of an acid, so pH is equal to pKa + logarithm of A-/HA, that is the undissociated form so there is a relationship actually.

So if you want to find out whether aspirin for example, it is an acid pKa is 3.5, the stomach has a pH of 2, blood has a pH of 7.4, so what is the A-/HA that is A-/HA pH is 2 so that comes out to be 10 raised to the power -1.5. So that means HA is quite large when compared A-, that means most of the drug is in the undissociated form, so it can get absorbed in the stomach, whereas if you look at the blood pH 7.4 A-/HA will become 3.9.

So HA is quite small actually so inside the blood it is dissociated, whereas in the stomach it is undissociated. So you have lot of undissociated part of aspirin, so it gets a reasonably absorbed from the stomach.

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$$pKb = pH + \log \left| \frac{\text{charged}}{\text{uncharged}} \right| \text{ for bases}$$

$$pKa = pH + \log \left| \frac{\text{uncharged}}{\text{charged}} \right| \text{ for acids}$$

Now what is the formula between connecting pKa, pH and so on for acids and bases, because we used that to calculate here. So pKa is given by pH+log of uncharged/charged for acids, that is why pH pKa uncharged and +log of uncharged/charged for acids, pK = pH of log of so when this goes that side you will get as - so you can put it as reverse. So pKa is pH+log of uncharged/charge for acids, whereas pKb = pH+log of charged/uncharged for bases. So we used this formula here, so pH is 2 so we use this formula.

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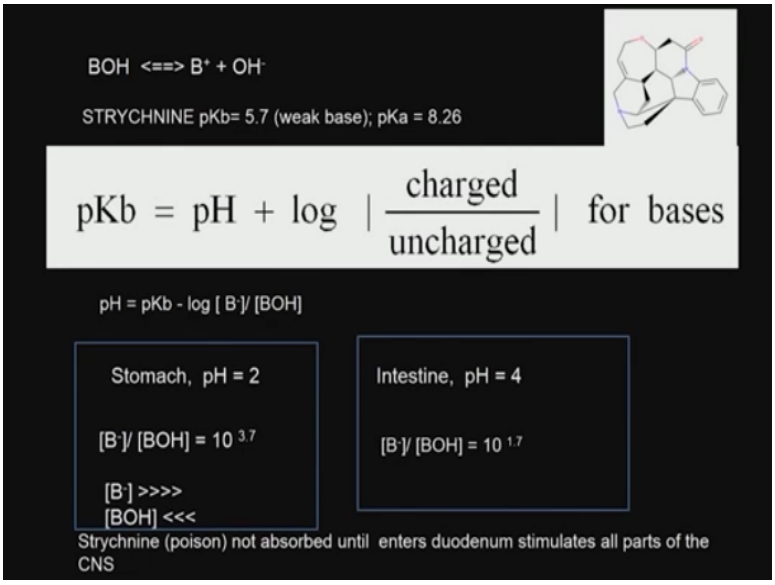

Now let us look at a weak basic for example. For a weak basic the BOH dissociates as B+ and OH- correct. So for example if you take this molecule, strychnine this is structure of this molecule. It is a poison; it is not absorbed until it enters duodenum, it stimulates all parts of the CNS. CNS is your central nervous system, so it is a poison. So pKb is 5.7, it is a weak base or pKa is 8.26 of the same, because pKa+pKb for the same system = 14 if you remember that.

So pKb=pH+log of charged/uncharged for bases. So we use that formula, then in stomach pH = 2, so what do we do B-/BOH = 10 3, that is 10 raise to power 3.7 approximately it could be 10,000. So B- is very large when compared to BOH when B - is large so it is a charged molecule so it cannot cross the lipid barrier. If you go to intestine pH is 4, so B- by BOH is 10 raised to the power 1.7, so you do have enough BOH so it gets absorbed in the intestine.

So as you can see here if you take aspirin which is weakly acidic, so pKa of 3.5 so it gets absorbed and then whereas this strychnine, it is got a pKb of 5.7 it goes down into the central nervous system to get absorbed. As we have said most acidic drugs are absorbed in the stomach so that is what happening, so aspirin gets absorbed in the from stomach whereas as I said basic drugs have to go down into the intestine to get absorbed like this strychnine.

So that is a very interesting strategy for designing quick-acting drugs slow-acting drugs by changing the pKa and pKb. And this is also very, very important for you to understand, because that will also tell you about the pharmacokinetics of the drug. If it is going to be

absorbed in the stomach, you will see the concentration rise very fast, quickly the concentration of the drug will rise in the plasma.

Whereas if it is going to get absorbed into the duodenum or small intestine the maximum concentration in the plasma will take much longer time.

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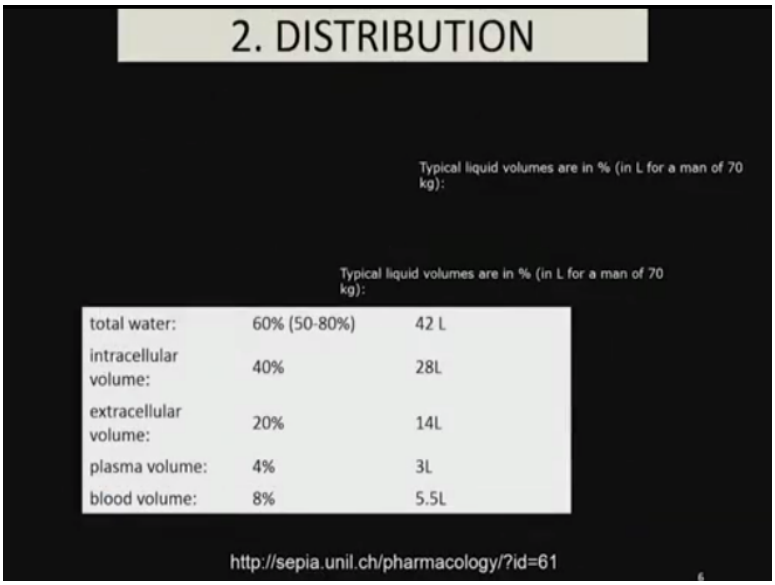

We have looked at the concept of absorption that is very, very important, distribution. Let us look at distribution. It is like I said a big pot, it is not only the blood even the tissues and other organs will be part of this big pot and the drug can get absorbed depending upon the molecular weight and lipophilicity and so on. So depending upon the several factors these contents of the pot may change. So when you drop some salt inside the pot it gets diluted.

So if the quantity of liquid inside the pot is very large, it will get diluted too much and the concentration will be very low. So the body is a vessel in which a drug is distributed by blood and it is not homogeneous. So it is not only the blood but many factors, typical liquid volume for a man of 70 kg, that is in percentages 5 major body components, the blood plasma, interstitial fluids, fat tissues, intracellular fluids, transcellular fluids.

Sometimes drugs get absorbed in tissues also, because if it is a very highly hydrophobic lipophilic it can go, so then your volume increases. So look at this, total water in the 42 liters, intracellular volume could be 40% 28 liters, extracellular volume 20% 14 liters, plasma volume 4%, blood volume 8%. So depending upon which contributes towards the absorption of the drug the volume can change.

So the volume can change depending upon the nature of the drug, depending upon health of the patient, depending upon the race, depending upon the gender and so on.

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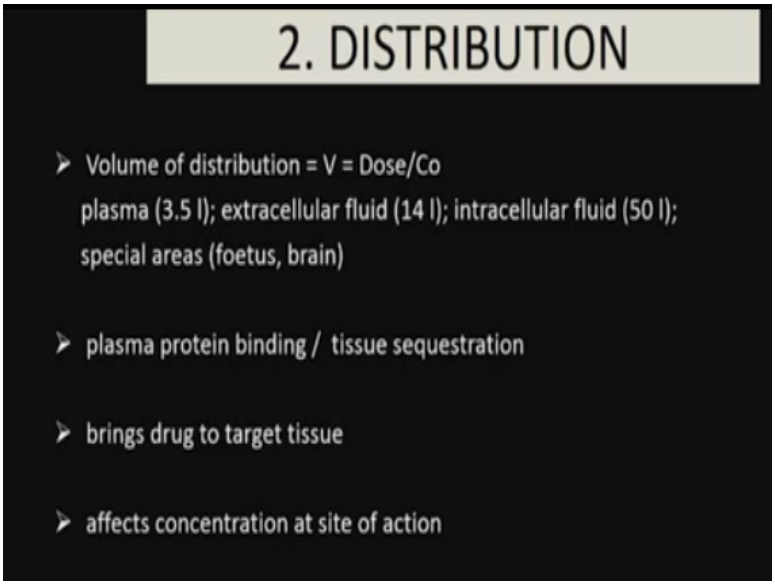

So volume of distribution, how much dose we give divided by C0. C0 is the maximum concentration the drug reaches in the plasma, I showed you, when you take oral drug, concentration keeps going up with function of time reaches a maximum and then starts coming down because of elimination and so on, that maximum concentration is called C0. So as you can see, if the volume is a very, very large C0 will become very small, if the volume is small C0 also become large, so they are indirectly related.

Plasma like I said 3.5 liters, extracellular fluid 14 liters, intracellular fluid 50 liters, even foetus, brain so they are all special regions where the drug also can get distributed. So the drug can go and bind to plasma protein it can go and bind with tissues that is called tissue sequestration, and then the drug starts, this is very, very important, because then the drug has to reach the target.

It is not like a small car which will just go directly to the target, but the drug gets distributed, get diluted and then it reaches the target. So the distribution affects the concentration at the site of action, like I said if the volume is very large concentration may be much low. So it might not be effective for it to act, an antibacterial drug should have effective concentration so that it is higher than minimum immunity concentration. If you are killing some cancer

cells the concentration should be higher than the cytotoxicity limits of the cells and so on actually.

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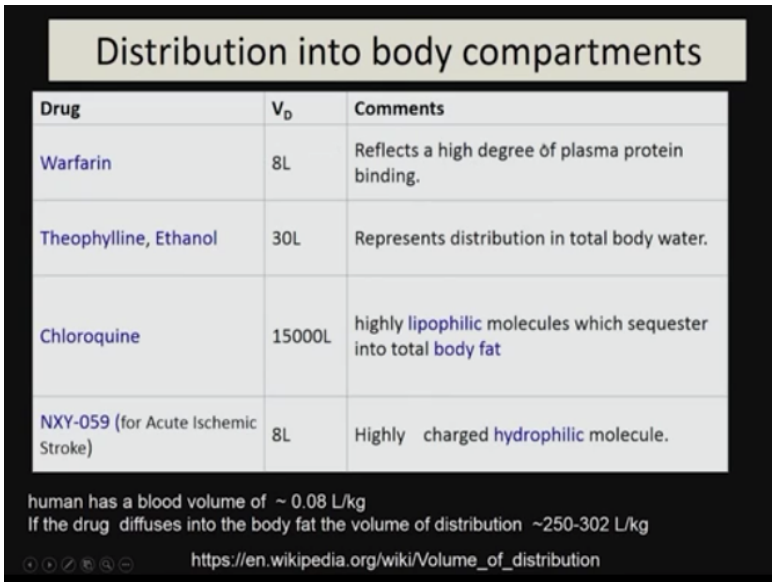

So for example warfarin, the volume of distribution is 8 liters that means there is only plasma protein binding involved. If you take ethanol, ethanol is a very small molecule. It goes everywhere. Theophylline 30 liters that means it represents distribution in total body water not only plasma, but also the body water. Chloroquine, this is a malarial drug, look at this huge, because it is highly lipophilic so it goes and goes into the body fat everywhere it goes.

That is why the volume, that is why the effective dosage the C0 will get very, very low, so you need to be given more chloroquine to achieve a considerable large C0. This is a drug for acute ischemic stroke 8 liters, because it is highly a charge that means hydrophilic, so it will not go into the fat then lipids and so on actually. So approximately human has a blood volume of .08 liters/kg.

So if somebody has about 60 kg person and he or she will have about 5 liters. If the drug diffuses into the body fat then the volume of distribution goes up to almost 250 to 300 liter/kg, as you can see here a very small molecule can diffuse into the fat and so on. So the volume increases dramatically and the volume increases dramatically, the C0 also will drop dramatically.

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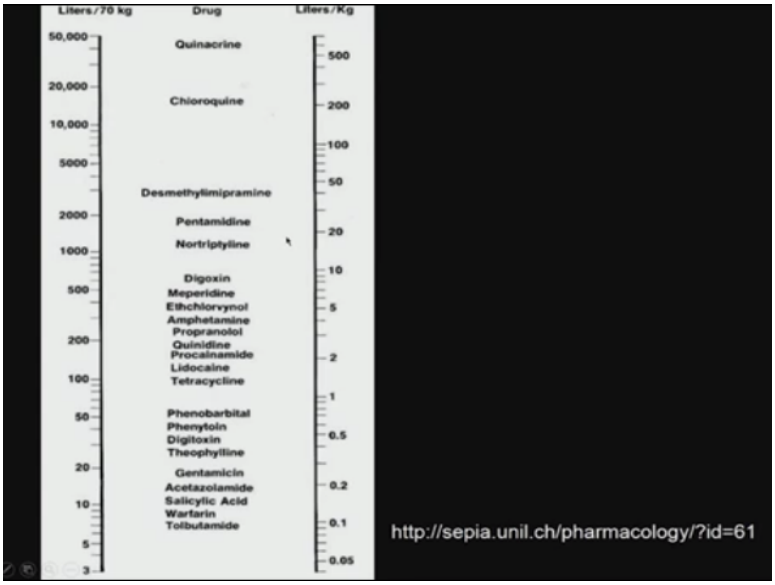

So as you can see here almost 3000 times like that you know. This is taken from this particular reference. So this is a very interesting graph because it tells you liters per 70 kg or liters/kg, the volumes for different drugs. So warfarin like I said all right down, so you can give even small dosage and C0 will be quite high, because volume is low. Salicylic acid because I see hydrophilic, theophylline, digitoxin, phenobarbital like that it goes.

Chloroquine this is your anti-malarial highly hydrophobic lipophilic, so the volume increases 20000 or 200 liters per. So highly hydrophilic polar groups volume will be low, lipophilic volume will be very large. So the drug gets diluted. This figure was taken from this particular reference.

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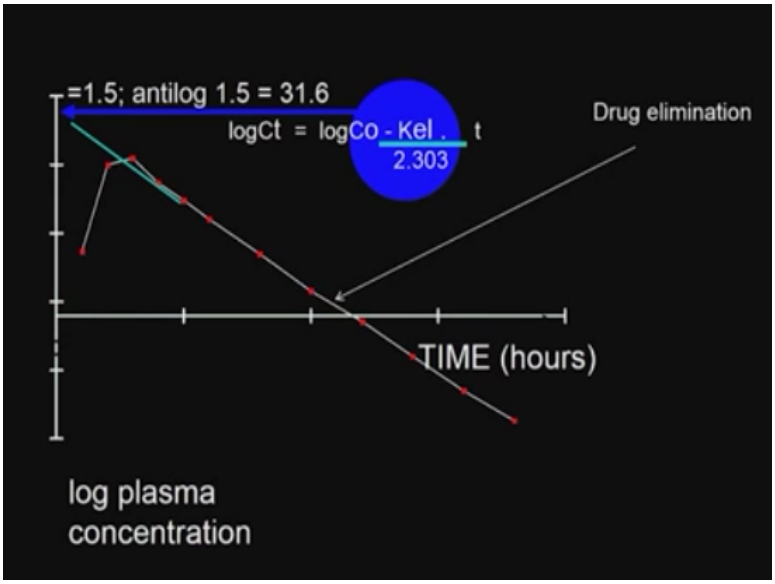

So this is the typical curve I have been showing you so if a person takes drug orally, this is the concentration, this is the time. So the concentration increases in the plasma, reaches and then it starts coming down because of elimination. And generally this equation we call it CT = C0 exponent -K elimination into time. So when we take logarithm to the base 10 then becomes logarithm of CT = logarithm C0 minus K elimination t/2.303.

So the slope of this line is given by this, K elimination, this is a negative slope because it is falling down. So here the axis is logarithm so when you take this and take an anti logarithm you get C0. So the distribution is a big pot where the drug goes and it gets diluted, so C0 goes down and the volume of distribution depends upon the body weight, volume of distribution depends primarily on the polarity whether the molecule is charged, small molecules.

So it can change by even a factor of 1000, that means C0 can come down by a factor of 1000 also. So it depends on the type of drug. So we need to understand that generally it is very difficult to tell what is the volume, but for standard drugs the data is available. So you can go to some databases and find out what is the volume of distribution like for some of the antibiotics volume of distribution and also I showed you in some of those drugs database drug DB and all that.

The volume of well-documented drugs or clearly stored so we can get those data very easily.

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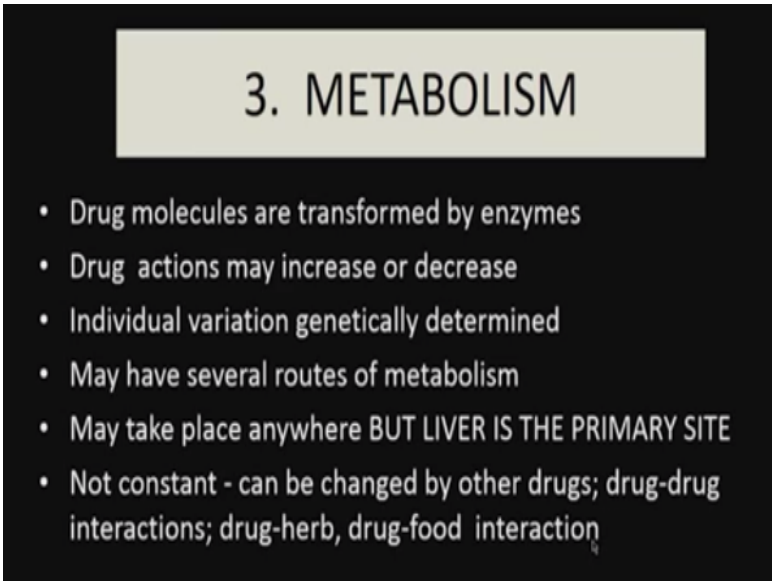

Then comes metabolism. So now the drug gets distributed. There is liver, there are so many enzymes in the body like oxidoreductases, lipase, estarace, hydrolase, amidace, so they start

degrading your molecule, so the molecule can become totally inactive or you may be forming new side products which may be toxic also. So metabolism is very important and again metabolism depends upon the race, depends upon the age, depend upon the health of the patient, depends upon whether the patient is taking other drugs.

So many factors affect metabolism. So metabolism for a Caucasian could be very different for it as against an Asian or against an African. So metabolism can be dramatically different. Drug molecules are transformed by enzymes, because body contains a lot of enzymes, and they have primary metabolism, secondary metabolism, so the metabolism is a very important activity in the body to remove toxic chemicals.

But unfortunately drugs also gets degraded during the process. So the drug action may increase or decrease, because you may form some products which are totally inactive. So there is genetic variation, a lot of genetic variation that has been seen. They said there are several routes for metabolism, but liver is the primary site but it can happen anywhere in the bloodstream that is very important. It is not constant.

There could be drug-drug interaction, drug-herb interaction, drug-food interaction. We take takes so much food and interestingly the drug and the food follow the same path. They go to the stomach and they have a passive diffusion goes to the bloodstream. They get metabolized, so they follow the same route, so there could be a lot of interaction between the drug and food.

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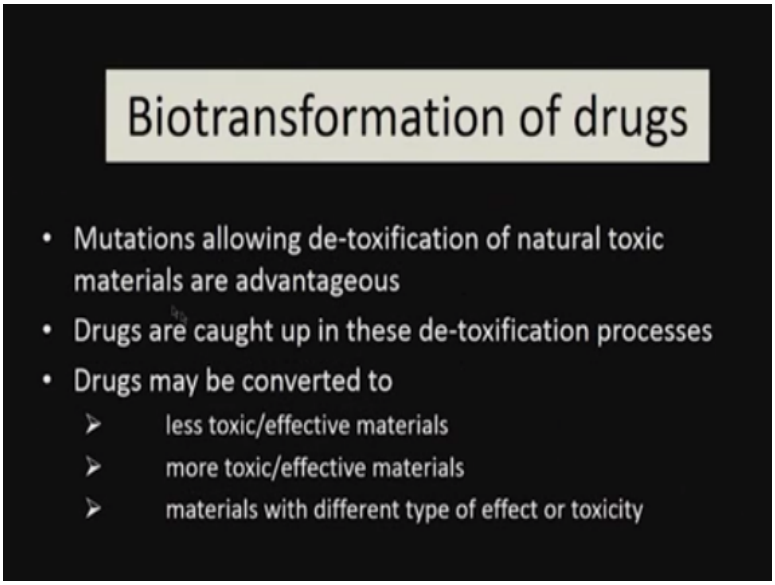

And mutations allowing detoxification of natural toxic materials are advantageous, because the body, this is a part of the defense mechanism in the body. As soon as the toxin is there may be a pesticide, herbicide or any chemical the body automatically tries to throw it out by transforming it into smaller molecule. So it is good, but unfortunately drugs are also caught up. So the drugs may be converted less toxic effective material, more toxic effective material, materials with different types of effect or toxicity.

So for example some drugs may get biotransformed and they may have some hepatotoxicity. So biotransformation is very important one needs to look at.

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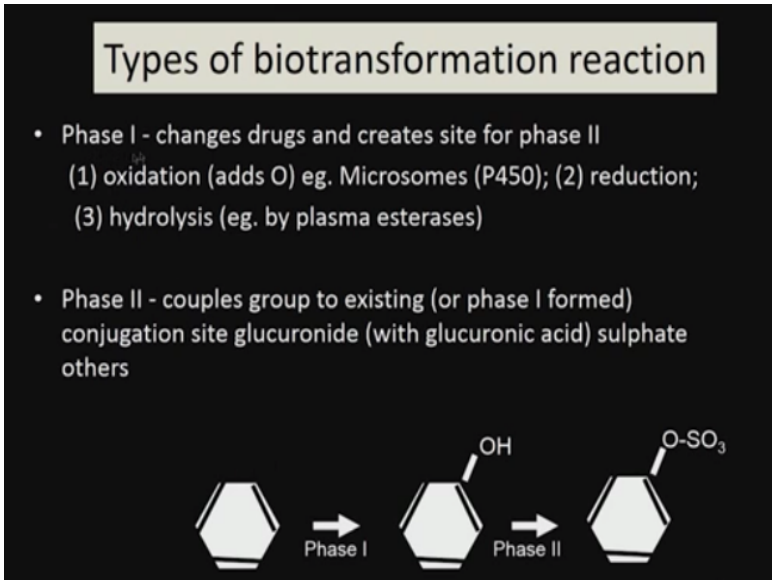

There are 2 phases of biotransformation, phase 1, phase 2. So the drugs changes and creates site for phase 2. So a phase 1 is a very simple metabolism. You do oxidation that means you are adding oxygen by using a p450 type of it. You do reduction, that means there is a hydrogen H added or O is removed, hydrolysis that means OH is added by esterases. In phase 2 groups are coupled, couples group to existing or phase 1 formed, conjugation site.

So glucuronide with glucuronic acid, sulfate another. So phase 1 you may be adding OH, because of this hydrolysis using an esterases, then in the phase 2 you are adding a SO3 group and this may be very easy to get thrown out from the body maybe through urine. Phase 1 is a simple process oxidation, reduction, hydrolysis. Phase 2 is for the existing groups conjugating with the glucuronic acid, sulfates and other things actually.

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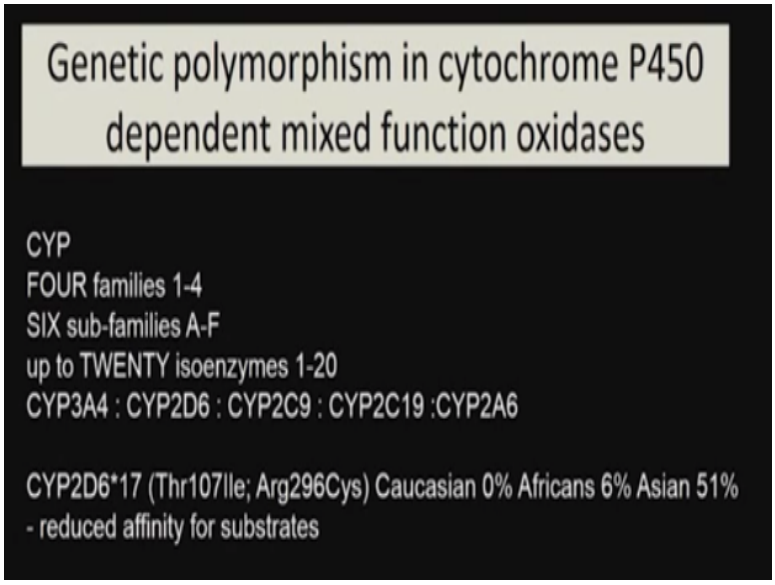

What does it do cytochrome p450 is one of the important things? It has 4 families 1 to 4, 6 sub-families A to F, up to 20 isoenzymes 1 to 20. So there are different cytochrome P3A4, P2D6 and so on actually. For example, if you look at this cytochrome CYP2D6 * 17, Caucasian will have 0%, Asian will have 51%, Africans have 6%. So there could be reduced affinity for substrates. So that is a problem, you have different amounts of some of these cytochromes.

So you may see different bio transformations between Caucasians and Asians you may see very dramatic differences actually.

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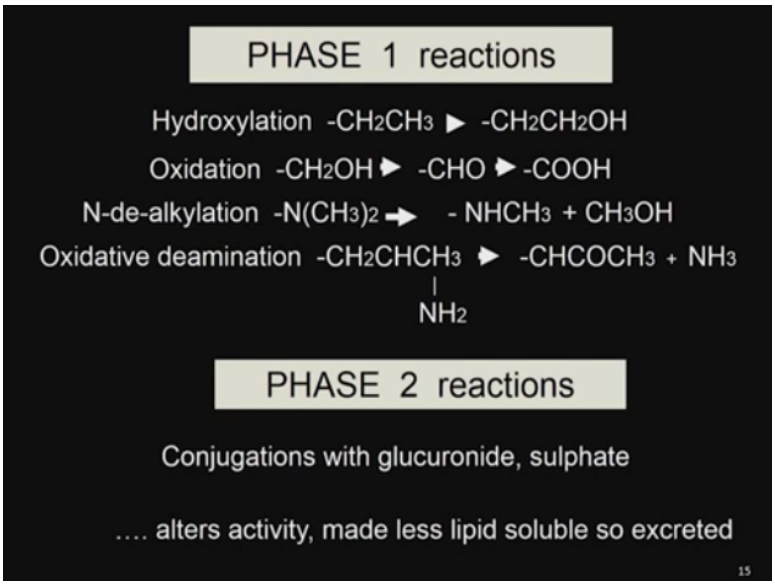

So the phase 1 reaction what happens hydroxylation, so you are putting a OH group here, CH2CH3 so you are putting OH. Oxidation, so we make COH or we remove a H here, so

CHO happens, even if you remove H it is called oxidation or we can add an O. de-alkylation, N-de-alkylation, that means you have a CH3 on the nitrogen which gets removed, 1 CH3 in the nitrogen is removed.

Oxidative deamination, so you are aminated, that means you are removing the NH2 group here into ammonia as well as you are putting a O, that is why it is called oxidative deamination. So hydroxylation, we are putting OH group or oxidation that means you may add an oxygen or remove a hydrogen, de-alkylation on CH3 from nitrogen is removed or oxidative deamination that means you remove the NH2 here and you may put a O here.

In phase 2 so you are conjugating it glucuronide, sulfate all these groups get conjugated. So it alters activity, it becomes more hydrophilic less lipid soluble, so it gets excreted, because you are adding sulfate and glucuronide and so it becomes more hydrophilic. So it becomes less lipid soluble so they get excreted that is phase 2. These are the 2 phases by which biotransformation takes place inside the body.

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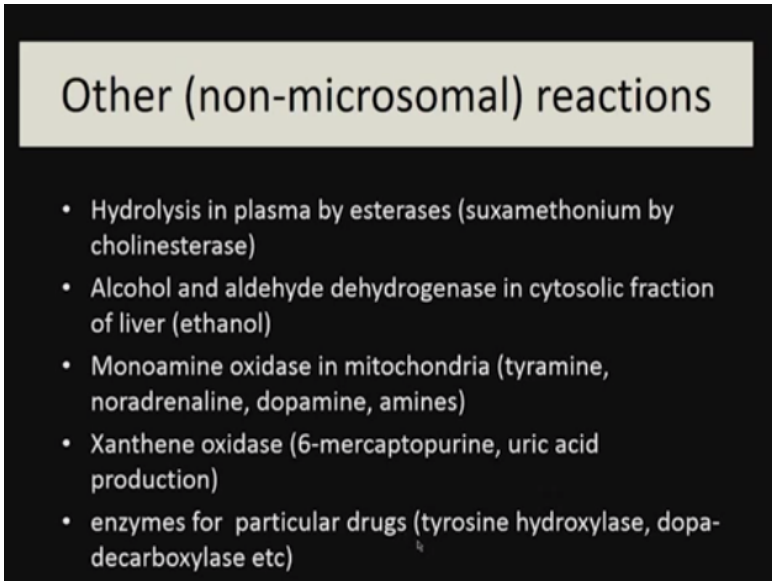

There are other non-microsomal reactions, hydrolysis in plasma by esterases. As you know esterases means esterification, like cholinesterase that is in the plasma not in the liver. Liver we have predominantly P450 type of enzymes. Alcohol and aldehyde dehydrogenases in cytosolic fraction of liver, ethanol if you have they get dehydrogenase enzymes dehydrogenated. Monoamine oxidase in mitochondria especially dopamine, amines and so on.

Xanthene oxidase, so these some of these enzymes which do the bio-transformation. Then there are enzymes for particular drugs tyrosine hydroxylase, dopa-decarboxylase and so on actually they are specific for different types of drugs. So in addition to changes that are happening in liver, we can also have changes in different parts like esterases, dehydrogenases, monoamine oxidase, xanthene oxidase and so on actually, tyrosine hydroxylase, dopa-decarboxylase, so all these can also act on your drug and modify its structure.

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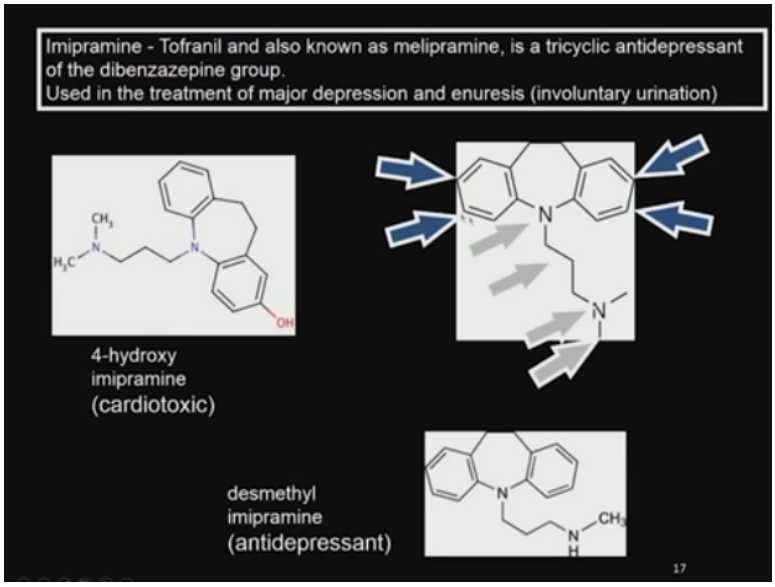

For example, let us look at this example, imipramine-tofranil and also known as melipramine, this is a tri-cyclic antidepressant of the dibenzazepine group actually, this is a tri-cyclic. This is used for the treatment of major depression and enuresis, that is involuntary urination. So what are all things can happen, you can have biotransformation in various places, this nitrogen, that nitrogen, here, here, here, here, here, here.

So when you do that for example, you put a OH, this becomes 4-hydroxy imipramine, it is a cardiotoxic, whereas if you remove one CH3 here and put an H, desmethyl imipramine becomes antidepressant. So depending upon the type of biotransformation, you end up with the product which can have a totally different effect, and look at this there are many sites for biotransformation.

So you can have groups put in here like OH, as I showed you or this nitrogen groups can leave or here the methyl groups can leave, so the product can be completely different and it can give a totally different activity.

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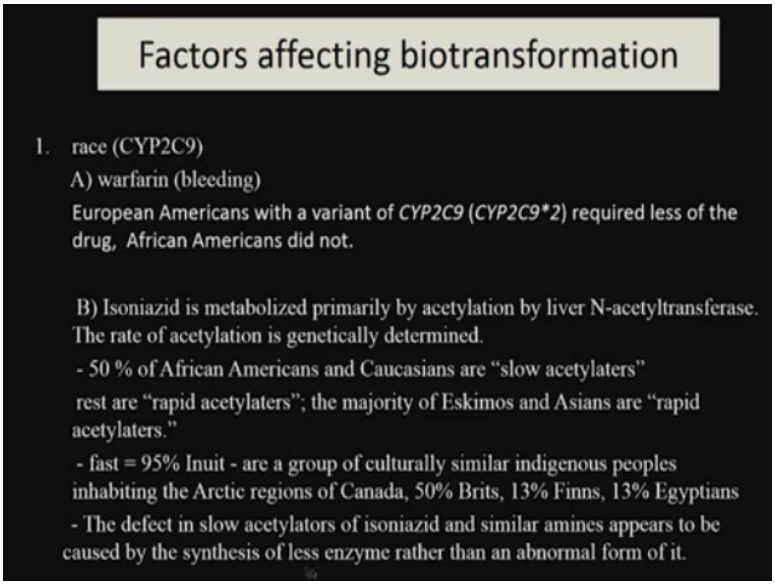

So what are the factors that affect biotransformation, race because CYP that is cytochrome P2C9 depends upon the race. Warfarin is used for bleeding European Americans with the variant of CYP2C9 require less of the drug whereas African Americans do not have that so did not, they require normal amount of drug that is an example. Isoniazid, isoniazid is used for tuberculosis is metabolized primarily by acetylation of liver N-acetyltransferase.

The rate of acetylation is genetically determined, 50% of African Americans and Caucasians are slow acetylaters, that means they have this drug present in the body for a much longer period of time. Rest are rapid acetylaters, the majority of Eskimos and Asians are rapid acetylaters, that means I need to keep giving the drug quite often because the drug half-life is very, very small, whereas African Americans or Caucasians I do not have to give this drug quite often.

Then you have fast very fast 95% Inuit, they are the group of culturally similar indigenous people inhabiting the Arctic region of Canada so you have different numbers of this. So the acetylation of this particular drug can vary depending upon the race. So why does it happen, the enzyme amount of enzyme that synthesized is very low so it does not get acetylation very fast, so that is the big problem actually.

Slow acetylation may lead to higher blood levels of the drug, so increase the toxic reaction. Drug will not be toxic in Asian that is fast-acting, but toxic in African Americans and Caucasians, so same drug, race plays a very important role.

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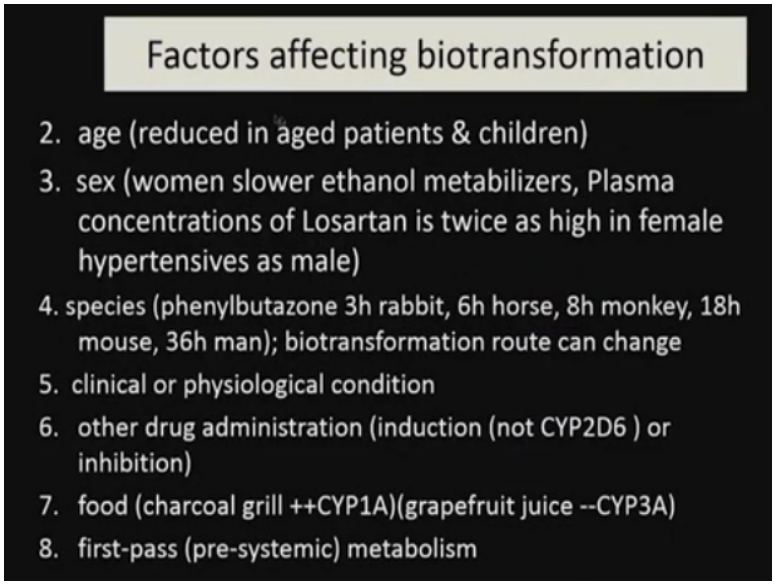

Next age, reduced in aged patients and children. So biotransformation is much lower in patients and children. So toxicity could be higher. Third is sex, women are slower ethanol metabilizers that is why the blood concentration of ethanol in women remain much longer than men, plasma concentration of Losartan is twice as high in female hypertensive when compared to male, this is a drug given for hypertension.

So species phenylbutazone eliminated 3 hours rabbit, 6 hours horse, 8 hours monkey, 18 hours mouse, 36 hours man, because the bio-transfer route can change. Clinical or physiological condition that means health of the patient, if the patient is sick or very healthy, the patient has undergone some operation, then other drug administration, that is whether some other drug is inducing or inhibiting certain enzymes.

Food like charcoal grill can affect because it produces a lot of amin, grapefruit juice it can absorb some drugs and started transforming it, first pass. So initially when the blood with the drug flows through the liver concentration is high, maximum biotransformation takes place when it comes back again the biotransformation levels are much lower. So we find so many factors affecting the biotransformation, and a drug can become toxic.

Because of the changes in the structural features, and a drug can be toxic if certain bio enzymes which bio-transform do not exist whereas it may exist in some other set of population. So the same drug or may be toxic in some population whereas it might not be toxic in some other population, the half-life of the drug may change in some population whereas it may be different in some other population and so on.

So we will continue more on this ADME in the next class as well thank you very much for your time.