Computer Aided Drug Design
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Lecture - 11
Drug - ADME

Hello everyone, welcome to the course on computer aided drug design. We will continue on the topic of ADME, A is the absorption in the GI, D is the distribution in the plasma and other tissues, M is the metabolism that may be taking place in liver and other parts inside, and E is the excretion.

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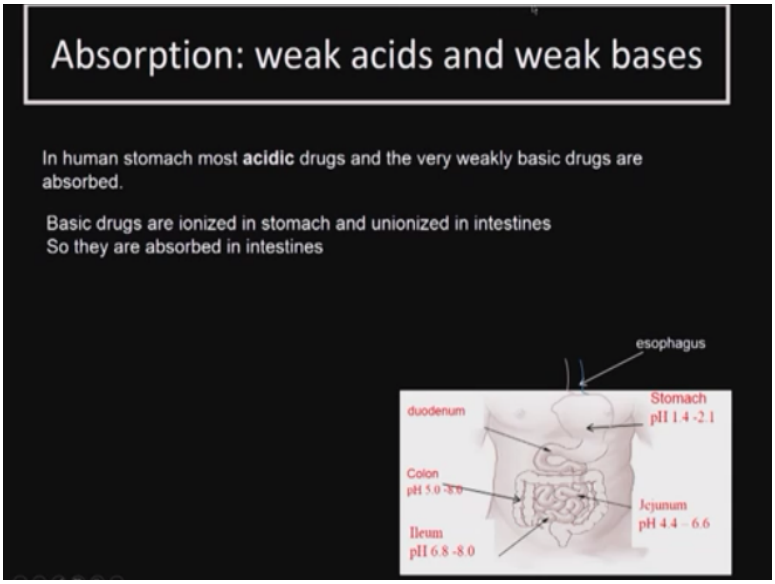

So we said absorption looked at the weak acids and weak bases because they are very, very important the pH inside the GI region changes tremendously. For example, if you look at pH in the stomach 1.4 to 2.1, then the drug may go duodenum, then it keeps traveling, jejunum where the pH is 4.4 to 6.6 and ileum pH is 6.8 to 8 and then colon 5 to 8. So there is a large variation in the pH starting from a highly acidic to basic.

So most acidic drugs and weakly basic drugs are absorbed in the stomach. Basic drugs are ionized in stomach and ionized in intestine, so they are absorbed in the intestine. So you need to design depending upon where you want the drug to get absorbed and especially if it is a quick fast acting or quick acting you want it to get absorbed here, slow acting you want to get absorbed down the line and so on actually.

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

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

So we introduced this particular equation for pKa related to pH, pKb related to pH and log of charged versus uncharged. So if you have charged molecule, they are highly polar. They will not cross the membrane barrier so ideally it should be in uncharged form, so that they can cross the lipid membrane barrier. More the charged it will be, it will not cross so that is the entire strategy of absorption.

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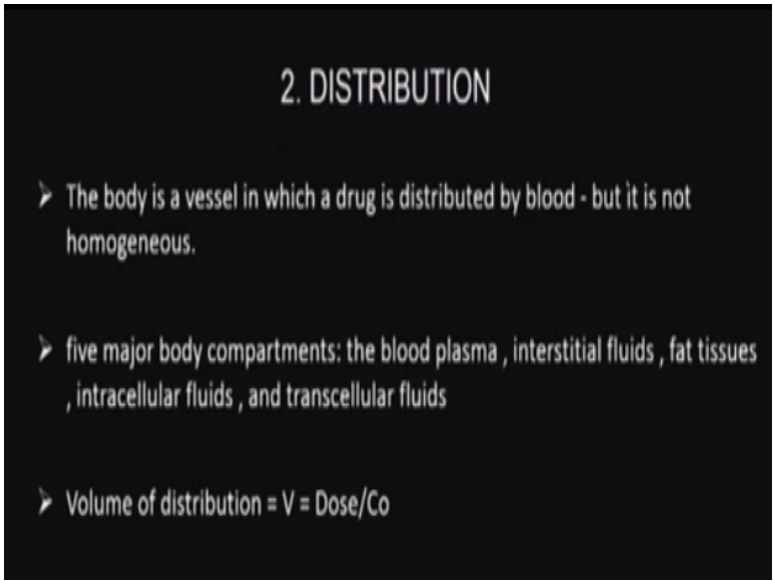

Distribution we said the body is like a big vessel, like a big pot containing lot of water, so the drug gets distributed and of course it is not uniform because you have plasma, we have the other tissues, so many different their intestinal fluids, fat tissues, intracellular fluids, transcellular fluids. So some drugs will get distributed only in the plasma. If it is a highly lipophilic, it may get absorbed in the tissue.

So the volume of distribution may change depending upon the type of drug and as I showed that the maximum concentration of that drug in the plasma will depend upon the volume of distribution, higher the volume of distribution lower will be that max concentration, lower the volume of distribution higher will be that concentration. So this equation volume = dose/C0, dose is the amount of drug we give.

So they are inversely related the volume and the maximum concentration it reaches depending upon the type of drug these will change and depending upon so many parameters the V can change.

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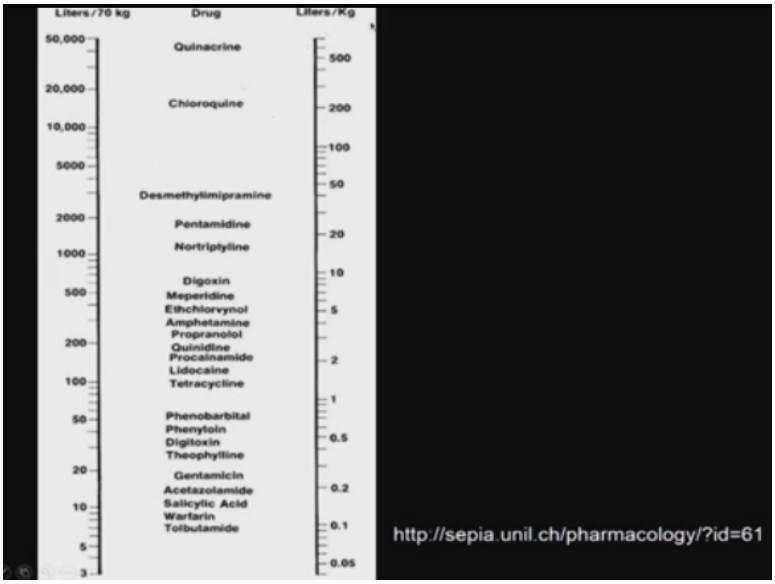

Then I also showed you a very interesting picture, taken from this reference warfarin for example, has a very low volume of distribution, whereas if you take a chloroquine which is a anti-material. Warfarin is a blood thinning, so chloroquine has a very high volume of distribution. So many drugs and alcohols, for example also have different volumes of distribution. So as the volume of distribution becomes higher and higher concentration also keeps going down and down actually.

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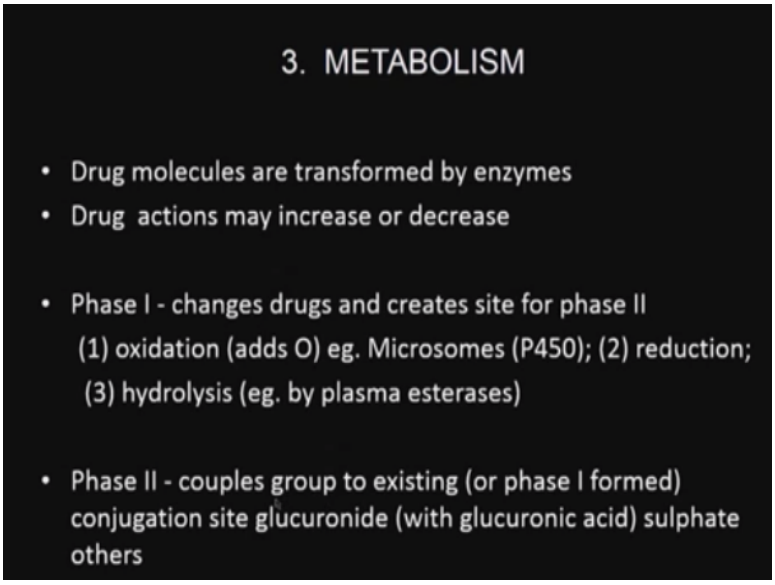

Then came metabolism because there is lot of biotransformation taking place inside the body especially in the liver and other places because of presence of a lot of enzymes oxidoreductase type of enzymes lipases, esterases, hydrolysis and there are 2 stages of biotransformation, stage 1 where either hydroxylation or oxidation-reduction takes place. And then other the second stage there are things like put sulfate type of groups get added.

So the drug action may increase or decrease, so the drug may be more potent or less potent you may be forming metabolites, which may be toxic, so all these issues can happen. So phase 1 changes drugs and creates site for the phase 2, oxidation, reduction, hydrolysis these are the 3 things that happen. In phase 2 what we have is couples groups to existing in phase one, so conjugation for glucuronide with glucuronic acid or sulfate and so on actually.

This is phase 2. So the compound becomes hydrophilic so it gets excreted in the urine. In fact, the metabolism is supposed to be good, so that the body is cleaned with the toxins, but drug also is viewed as a toxin and gets metabolized.

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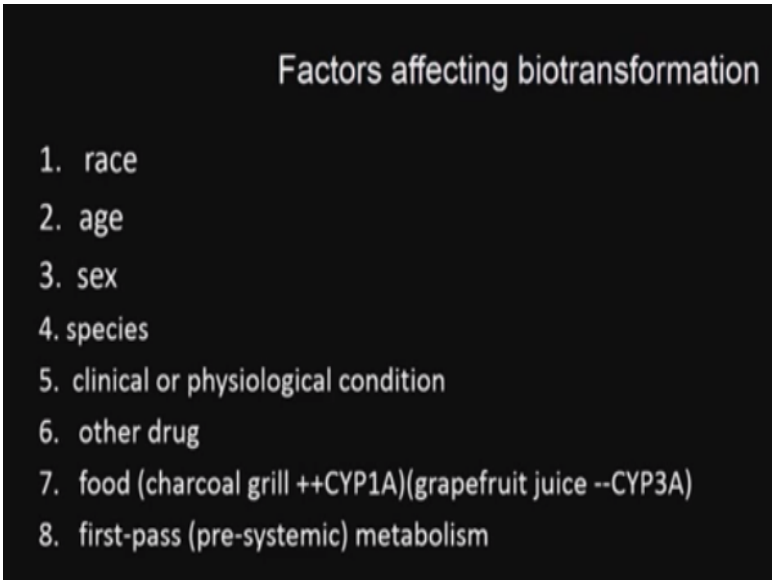

Many factors affect this bio-transformation race, age, the sex, the species. Monkeys may have different metabolism as against horses or animal like rabbit or human. Clinical or physiological condition, sick patient, healthy patient, if you are giving other drugs those drugs may be acting on these drugs and then getting metabolized. Food, whatever food we are eating for example, charcoal grill, grapefruit juice.

So it enhances some cytochrome P when a charcoal grill gets, grapefruit juice CYP cytochrome P3A. So the metabolism will get affected depending upon the type of food. Now first pass metabolism, that means when it goes through the liver of the first pass, you see lot of metabolism and after that it reaches a steady state.

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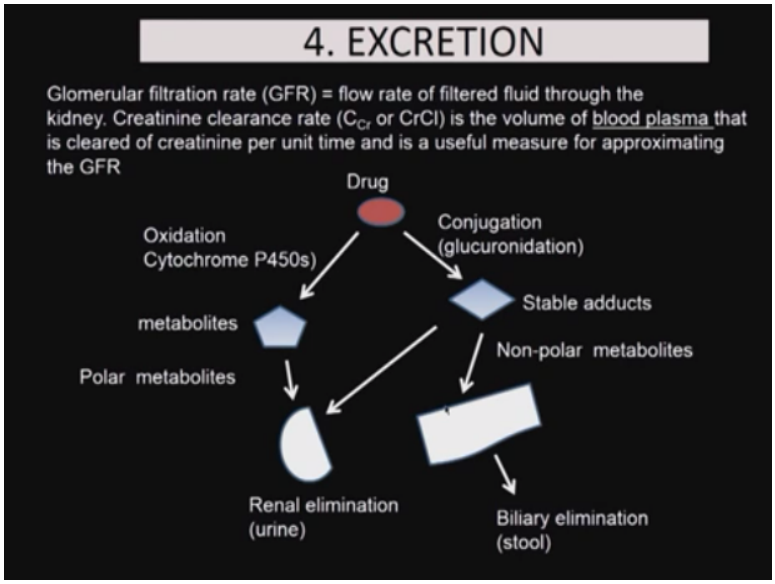

So absorption, distribution, metabolism, excretion is the 4th. You have a glomerular filtration rate GFR. Glomerular flow rate of filtered fluid through the kidney, so this is called a GFR. Creatinine clearance rate that is CCR or CrCl is the volume of blood plasma that is cleared of creatinine per unit time. This is a very useful measure of understanding GMR. So how much of creatinine gets removed per time from the blood plasma.

So that tells you this GFR. So you have the drugs, we have an oxidation or conjugation, so you may find metabolites stable adducts. So if it is polar, immediately it goes through the renal urine, if it is non-polar these are stable adducts it may go into the biliary elimination stools. So this is how the drugs get excreted from the body. So we have oxidation, conjugation, some stable products, metabolites, because these are all polar it gets removed in urine, non-polar it goes it will get removed in stools.

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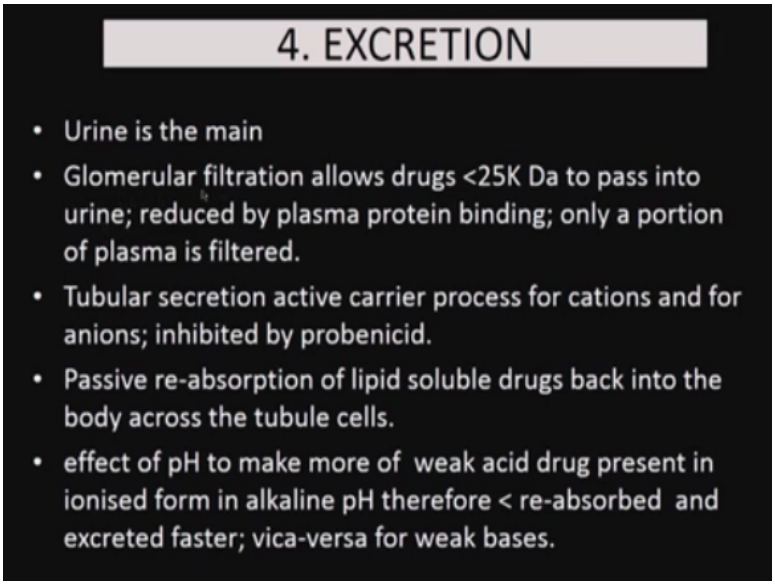

So generally urine is the main. The GFR glomerular filtration removes all drugs below 25,000 and as you know most of our drugs are around molecular weight of 500 dalton or less. So chances are drugs can nicely get excreted through urine, reduced by plasma protein binding only a portion of plasma is filtered. Tubular secretion active carriers process for cations and for anions, and inhibited by probenicid. There is a passive re-absorption.

So as it tries to come out, there could be again re-absorbed of lipid soluble drugs back into the body across these tubule cells. So it gets excreted and there is a passive re-absorption of some of the lipids molecule. Effect of pH to make more weak acid drug percent in ionised

form in alkaline pH, therefore it is less reabsorbed and excreted faster. So if you have more weak acid drug present in ionised form in alkaline pH, chances are it will not get re-absorbed.

So they will excrete faster and same thing vice versa for weak bases. So if you have weak bases chances are it can get re-absorbed.

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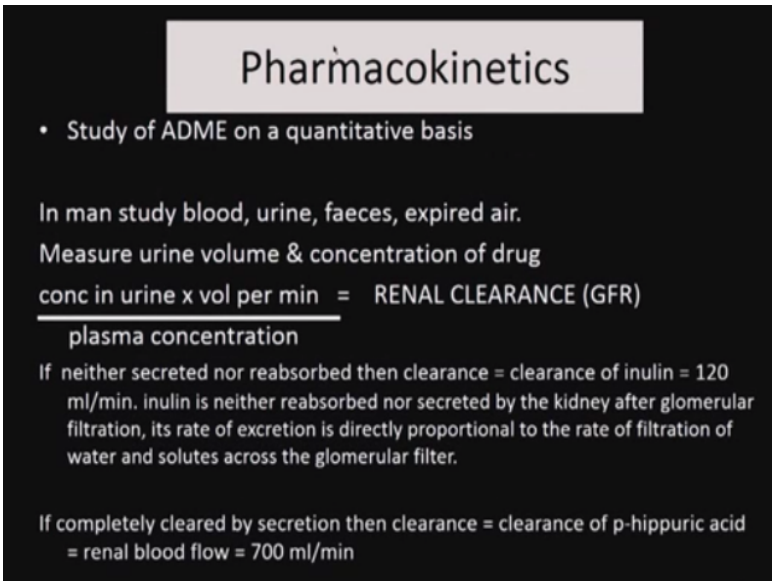

So you have something called pharmacokinetics which studies this entire ADME in a quantitative manner. So what do we do. In human, we look at the blood, we look at the urine, we look at faeces, we look at expired air, and then we find out concentration of the drug, and then we see how the drug gets removed from the body. So concentration in urine into volume of urine per minute/plasma concentration, that is called renal clearance.

Concentration in urine, volume that gives you total amount of drug that is getting removed in urine/plasma concentration that is a renal clearance. If neither secreted nor re-absorbed then clearance is equal to clearance of inulin, that which is 120 ml/minute because inulin is neither re-absorbed nor secreted by the kidney after glomerular filtration. So its rate of excretion is directly proportional to the rate of filtration of water and solutes across the glomerular filter.

So we can use inulin to check how good the system is in excreting it. If completely cleared by secretion, then clearance = clearance of p hippuric acid that is renal blood flow which is around 700 ml per minute. So these parameters are very, very useful to understand the system, how the urine, the kidney works and how the clearance in the urine happens, and it also gives you a measure of GFR.

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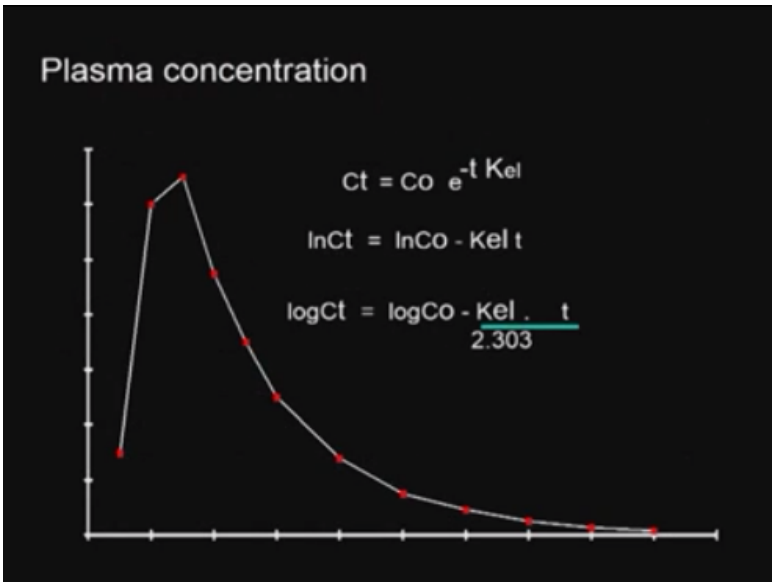

So if you monitor the drug in the plasma, if it is given as a oral drug, the drug concentration increases the x-axis is your time, y-axis is your concentration, so it reaches a max and then starts coming down because of excretion. So we can write first order relationship Ct concentration = C0 that is the maximum it reaches. So we can if you extend it C0 e power -t Kel, K elimination that is called the rate constant of the elimination.

If you take ln of both you are going to end up with the ln K elimination, if you take logarithm, this is with base 10, this is with base e, we end up dividing by 2.303.

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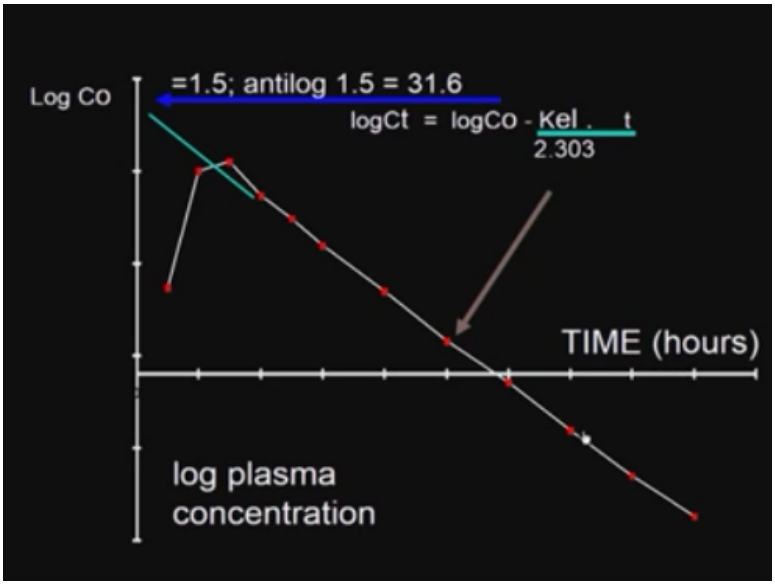

So what do we do, we extend this right up to the end. If you have the x axis as time, y axis as logarithm C0, rather than ln, then we draw this line extend it and see where it touches. And

you take anti-log that will be your C0, and then this slope will be your K elimination. So we get both the C0 and K elimination, so this is a very useful relationship to understand how the drug concentration falls down at plasma.

We can even calculate what will be the half-life of the drug, that means the concentration comes to half its max concentration, time it takes for the concentration to reach that we can find out.

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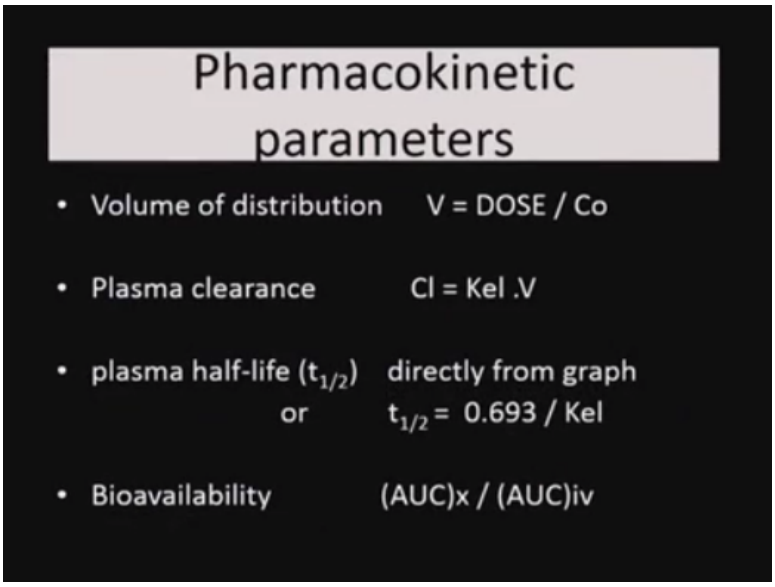

So these are very useful pharmacokinetic parameters. In addition, we can calculate volume of distribution dose/C0, that is C0 is this. We know how much dose we gave; plasma clearance K elimination is nothing but the slope of this line into volume that is plasma clearance. Plasma half-life that is how long it remains t half = 0.693/K elimination, bioavailability is the area under the curve, if it is given as oral divide by area under the curve and it is given as IV that gives you bioavailability.

So from this graph we can do a lot of calculation. So we extend this and then from there take anti-log, we get C0 and this slope will give you K elimination, volume of distribution is dose/C0, plasma clearances Cl = K elimination * volume, which you get from here, t half plasma half-life time 0.693/K elimination, if you have this similar graph when it is given in IV form area under the curve in oral divided by the area under the curve in IV form.

Like I said generally bioavailability has to be very high and so that the concentration at the target site is good, the efficacy of the drug is good, we do not have to give too much dose of drug so possibly toxicity also can be lower.

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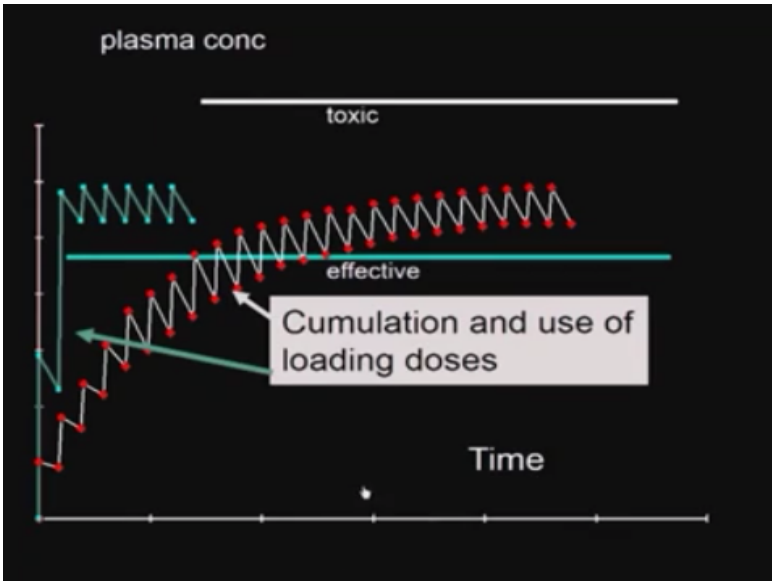

So if you have multiple doses so there is going to be some accumulation. Accumulation of this drug may be in the tissues or it is not fully removed from the plasma. So you may have this type of up and down. This is a loading doses. That is why sometimes the first dose or second dose may not be effective, but third, 4th doses become effective because there is a slow buildup of the drug because of maybe tissue absorption then further there is desorption and so on actually.

Of course you need to watch out if you know the toxic limit of the drug, you work within the toxin, below the toxic limit. So if you have the effective range and toxic, this will be nice to operate within which effective could be if you are looking at anti bacterial, you know minimum NB3 concentration, so you want the drug all the time to be above that MSE but it should be less than the toxic limit.

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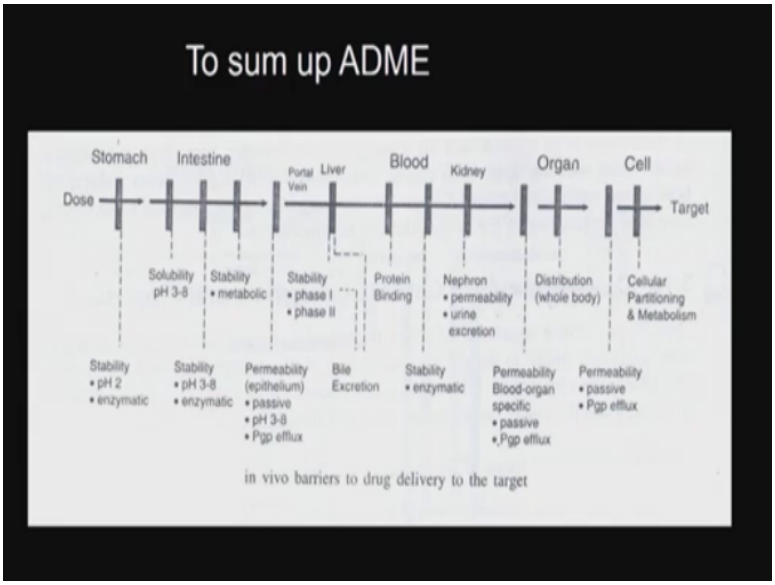

So to sum up ADME, we have the dose given orally, you have the stomach pH is 2, we are talking about stability at these conditions and then there are enzymes which may degrade the drug then solubility that the drug has to be soluble pH or a wide range. Intestine pH has become bigger. It has to be still stable, then of course you are forming metabolites. They have to be stable, then we have the permeability. That is it is crossing the barrier.

So permeability, we talked quite a lot about permeability what is important in log P, generally it is passive type of permeability just like food, pH is big. We have something called Pgp efflux. I will talk about this later the Pgb efflux and there are P glycoprotein which will throw the drug out. So those things we will talk about it. Then of course my, the metabolism, phase 1 metabolism, phase 2 metabolism and then you could also have proteins binding.

There are if you have acidic drugs, protein binding could be a big problem. Then apart from liver you need to consider other enzymes present in the body whether your drug gets stable or not, and then of course the kidney, the urine excretion comes into the kidney permeability all those coming to the value. And then permeability to the specific site again through passive you can have again Pgp efflux coming into that means P glycoproteins may be throwing your drug out and that will lead to reduction in its concentration.

And then this distribution, volume of distribution which we talked about, which can alter the concentration of the drug in the body. Then again we have the permeability, then cellular partitioning, if the drug is going in the presence of cells there could be partitioning of the

drug, metabolism happening and finally reaching target site. So a lot of steps before which the drug goes, reaches the target sides and exhibits bio-activity.

So the bio-activity is not disturbed, but the bio-availability and stability, solubility and all these factors are disturbed because of presence of all these environmental changes as well as the presence of enzymes and so on. The activity does not get modified; efficacy can get modified because the drug can become less efficacy, because of the metabolism of the drug, formation of new molecules and so on.

So this entire set of steps affect the drug action overall that is why many drugs when they go into clinical trials whether it is animal or human fail, although it may have shown very good activity in the lab in enzyme assays or some bacterial assays and so on.

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There are many rules, many models, rules which give a feel of whether a drug can be bio-available, orally bio-available whether it will satisfy all these conditions like good solubility and a good GI penetration and so on. There are many rules. So we can have a look at some of these rules and when you have a new compound designed, you can check it out whether it will satisfy all these rules or whether it does not satisfy all the rules.

If it does not satisfy and if you feel there could be some problem, you need not take that particular compound for activity selection. So we can use these rules also for screening as large number of molecules, that is what we do.

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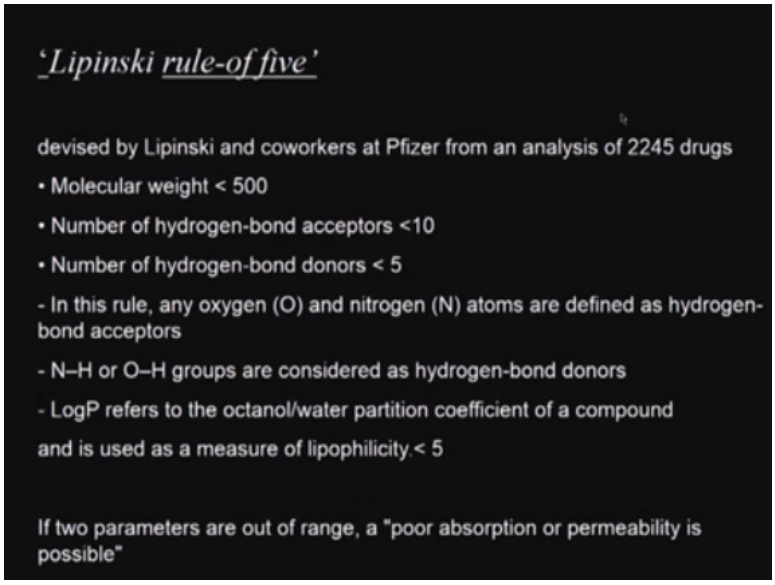

The very well studied, well understood, well considered is called Lipinski's rule of 5. Lipinski and his co-workers at Pfizer looked at a large number of drugs, that is drugs which have sort of accepted by FDA and passed the FDA, and so they picked up and they said all these drugs satisfy certain conditions. The first one is molecular weight less than 500, so they said you should have molecules, which are reasonably small less than 500.

You cannot have very large molecule. Please note this is for oral. This rule is, all the rules I am going to talk about is for oral drug and not for IV or IP and so on. Number of hydrogen bond acceptors <10, that is oxygen and nitrogen are defined as hydrogen-bond acceptors. Please note if you have an acidic O-, then it will not be an acceptor, but oxygen and nitrogen are defined as hydrogen-bond acceptors.

Hydrogen bond donors that is NH or OH should be <5. These are very important because these determine the hydrophilic, lipophilic nature of the molecule plus also how they go and bind with the various enzymes. So number of acceptors should be <10, number of hydrogen bond donors should be <5 and log P which I defined that is the octanol water partition coefficient should be <5.

That means if it is more than 5, you are talking about a molecule which is very hydrophobic, and if it is <0 or less, then we are talking about a molecule which is very hydrophilic. So both we do not want, so according to them it should be in this region, but there are rules which narrows this region also. So according to them if 2 parameters are out of range, and then

chances are, it will definitely have a poor absorption or permeability, and bio-availability also will be low, so do not take up that molecule.

If 1 of the parameters are bad chances are maybe it may have reasonably good GI absorption, but if 2 do not, so that is the rule. So molecular weight <500, the number of hydrogen bond acceptors <10, number of hydrogen bond donors <5, log P<5, that is 0 to 5, this is called the Lipinski's rule of 5. Similarly, there are many rules as I said we are going to look at some of them.

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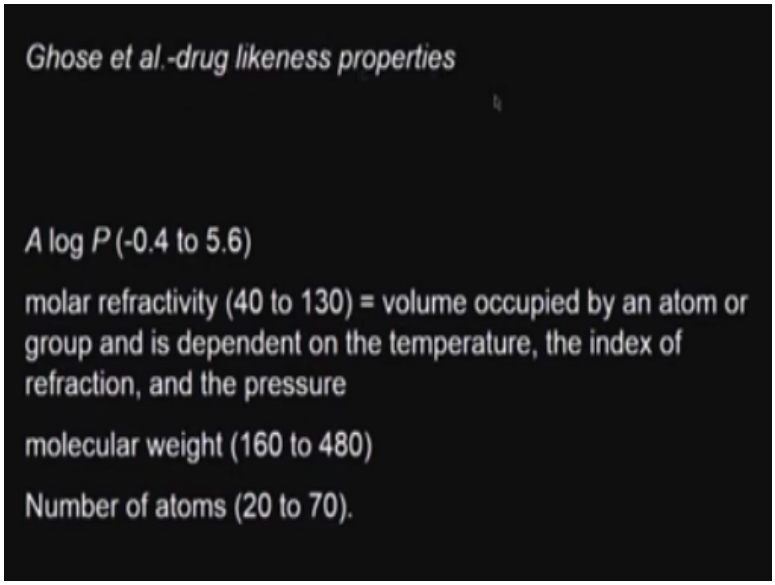

We have another rule called Ghose et al, this called drug likeness property. So they came up with again log P. There are many prefixes M, A, so these are calculated using different softwares. So this gave little more range -0.4 to 0.6, molar refractivity between 40 to 130, so they brought in a new parameter. This is the volume occupied by an atom or group and is dependent on the temperature, the index of refraction and the pressure.

This is a volume occupied. So they bring in the volume between 40 to 130, molecular weight look Lipinski said <500 whereas they are bringing 160 to 480. They also bring number of atoms 20 to 70. So they have made some changes, they came up with new set of parameters or descriptors we call it parameters, descriptors, features of the drug. This is called Ghose et al drug likeness property.

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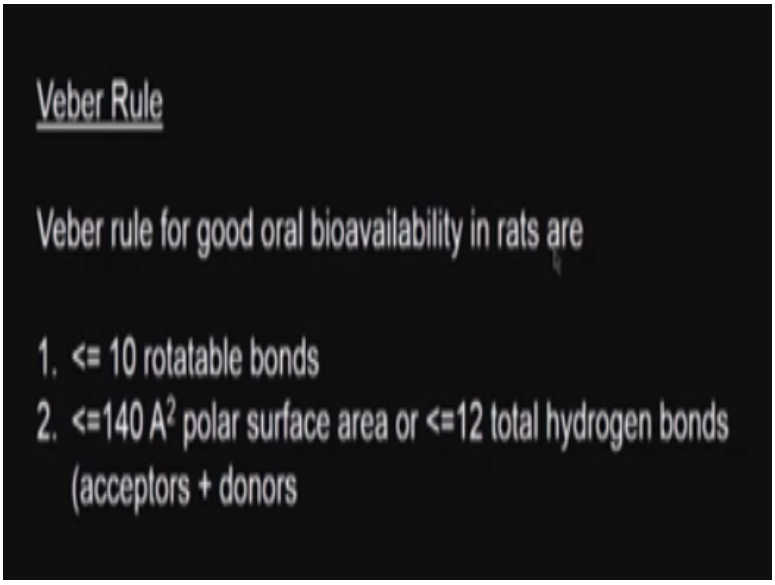

Then there is a Veber rule, Veber rule for good oral bioavailability in rats. They said <= 10 rotatable bonds, why rotatable bonds are important because if you have more rotatable bonds, it can take up different confirmations and so the binding with proteins have large degrees of freedom. The polar surface area should be < 140 angstrom square, if it is more, then of course it becomes more hydrophilic, it will not permeate through the GI.

Less than 12 hydrogen bond acceptors + donors. So they did not differentiate between hydrogen-bond acceptors separately, donor separately like Lipinski's. This is called Veber rule.

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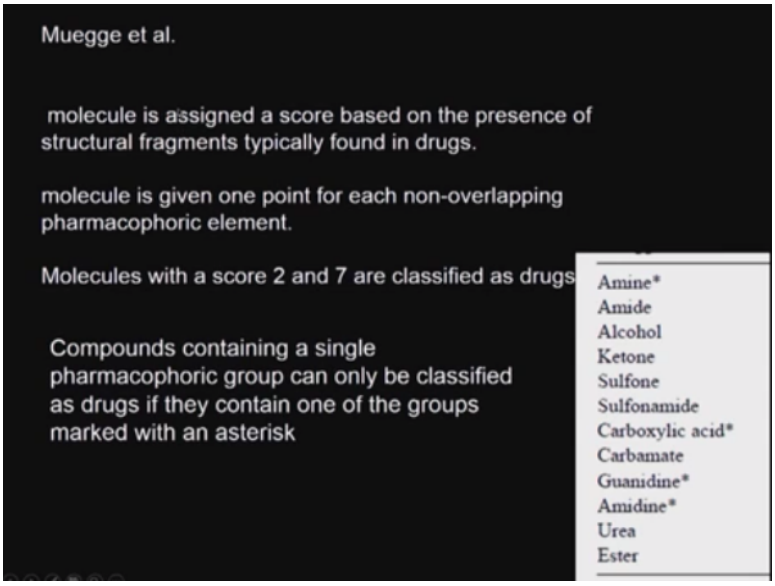

Then comes another rule that is Muegge et al rule. So what they did was, they looked at a molecule and saw whether it had these type of functional groups, amine, amide, alcohol,

ketone, sulfone like that you know. So they gave a score based on the presence of a structural fragment typically found in drugs. So they say drugs will have only these groups ester, urea, amidine, guanidine, carbamate, carboxylic acid, sulfonamide, sulfone, ketone, alcohol, amide, amine.

So you give 1 mark for that, give 1 point for each non-overlapping pharmacophoric feature that means if it has got 2 ketone groups do not give 2 marks just give 1. So molecule with the score of 2 to 7 are classified as drugs. So look at your molecule and see how many these groups are present, so you give 1 mark for each of this non-overlapping and if it falls between 2 and 7, then you classify as drugs.

These groups even if it is present 1 compounds containing a single feature of carbolic carboxylic acid or amine, then you can classify it as a drug, even if it contains single feature, that is there. So how did they do it, they looked at the various functional groups present in all the commercial drugs approved in FDA oral drugs and then they said we will give 1 point for presence of each of this non-overlapping group and if the score is between 2 to 7, you can classify it as a drug.

If the compounds contained this single, even if it contains 1 single feature then we can also classify it as a drug, that is called Muegge rule.

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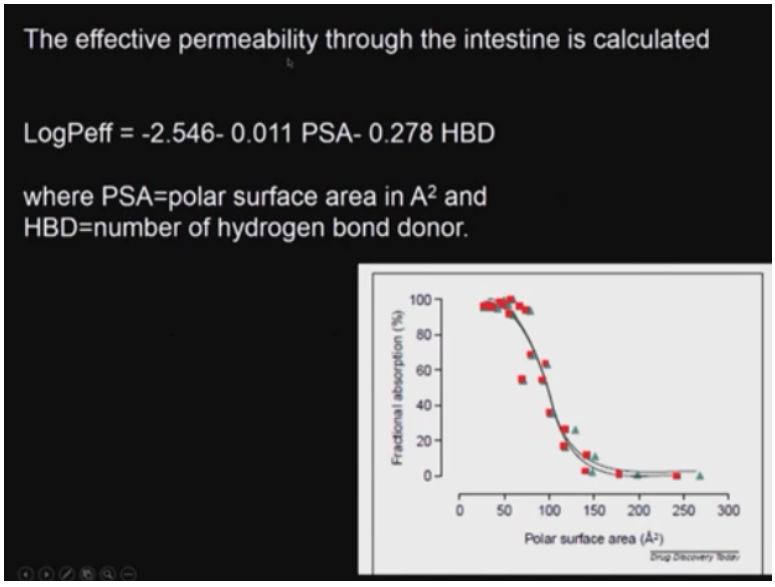

And the effective permeability through the intestine is calculated from this equation log P effective, PSA is polar surface area, HBD is hydrogen bond donors, hydrogen bond donors

means OH or NH. So this figure was taken from this reference. As you can see, as the polar surface area is low that means it is lipophilic, the absorption fractional, the absorption in the intestine is very, very high.

And as the polar surface increases that means it becomes more hydrophilic then it dramatically falls down and it comes to very low value when the area polar surface area is above 140 angstrom square. That is why as you can see in 1 rule we said it should be < 140 angstrom square, but ideally it should be <100, so that you have absorption at least 50%. So polar surface area should lie in this region that means lipophilicity is good but of course we do not know whether solubility will be good if you have more lipophilic.

So you want to work in this region at the same time have a soluble molecule, you do not want to work in this region. So that is the based on polar surface area and hydrogen bond donors trying to look at how the effective passive permeability will be through.

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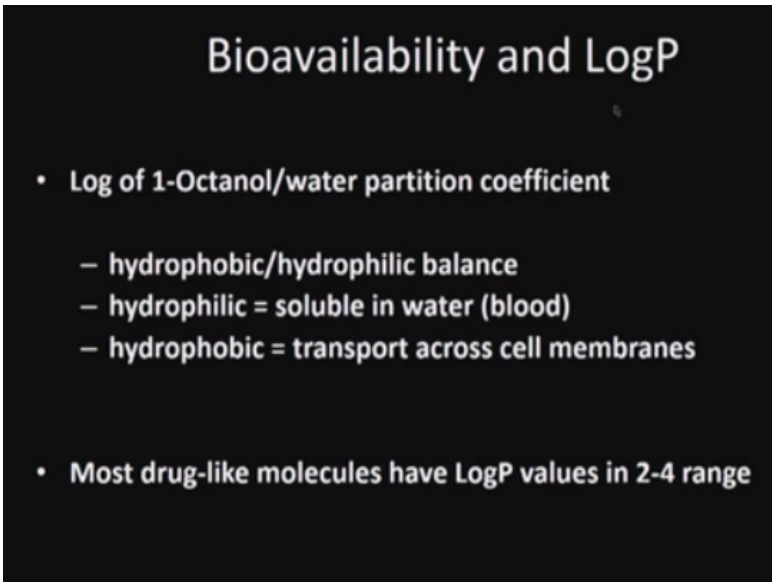

Then came log P as I said log P plays is a very important role, log P is octanol water partition coefficient, it gives a hydrophobic, hydrophilic balance. Hydrophilic means soluble in water and blood. Hydrophobic means soluble in the lipid and it gets transported across, and most of the drugs have log P between 2 to 4, 4 or 5 highly hydrophobic, you have some anti fungal drugs having very high log P.

If the log P is very low it is highly hydrophilic, it might not cross the barrier so it may be given in the form of IV.

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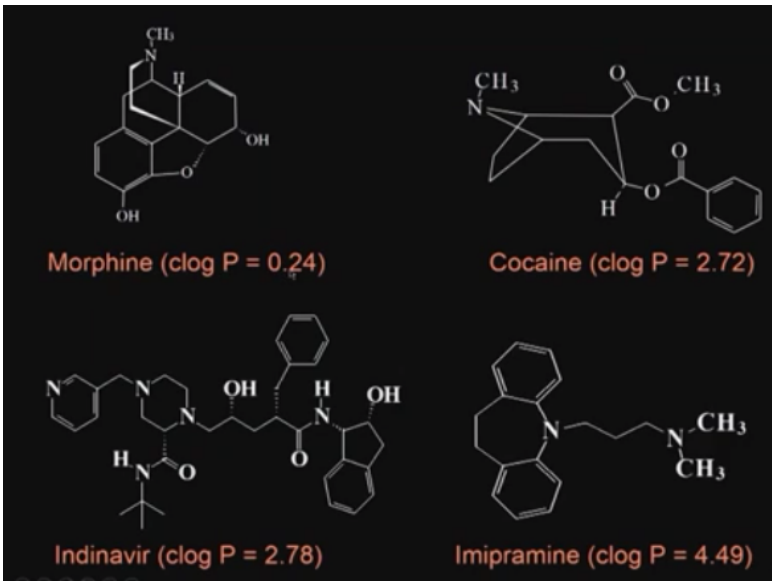

Look at this Morphine very low log P, highly hydrophilic. You have so many OH groups here, nitrogen so it is always given as IV. As I said C or M, they are all using different software actually. Cocaine 2.72, Indinavir 2.78, Imipramine high log P, because it has got only 2 nitrogen hydrogen-bond acceptors, otherwise lot of CH2, highly hydrophobic molecule here.

Although this has got many O's, it also has got many CH2 groups here the benzene rings and so on actually, that is a log p is not really bad.

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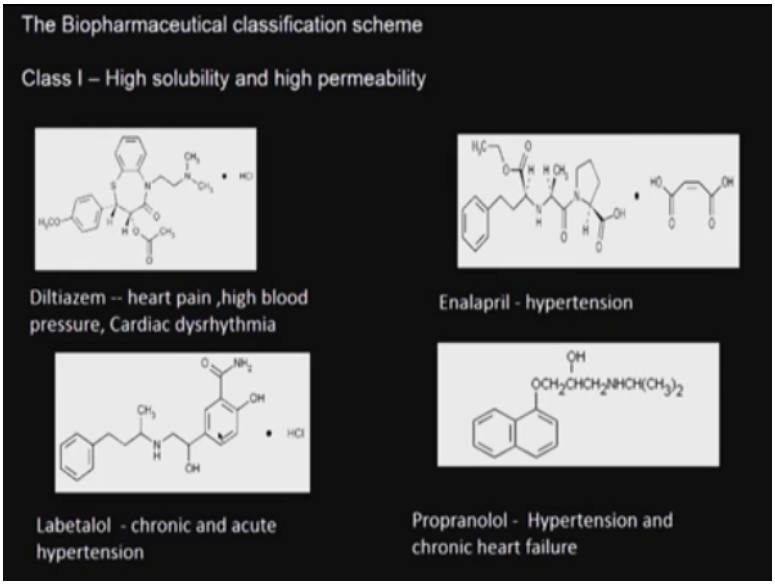

The bio-pharmaceutical has classified drugs into 4 categories, it is called a highly soluble highly permeable, then we have a poorly soluble highly permeable, highly soluble poorly permeable, poorly soluble poorly permeable, so 4 classifications. The highly soluble highly

permeable there is no problem, drugs will nicely get solubilized in GI, and they will also nicely pass through the membrane.

For example, look at this Diltiazem, this is a heart pain, high blood pressure, cardiac arrhythmia and so on. So it is got a highly soluble highly permeable, so it is got a lot of hydrogen-bond acceptors there, at the same time it is got a lot of CH2 so it is nicely balanced. Enalapril, this for hypertension this also highly soluble highly permeable. Labetalol is chronic and acute hypertension, these are all salts as you can see here, salts.

Propranolol, hypertension and chronic heart failure, so these are coming under class 1 highly soluble and highly permeable drug.

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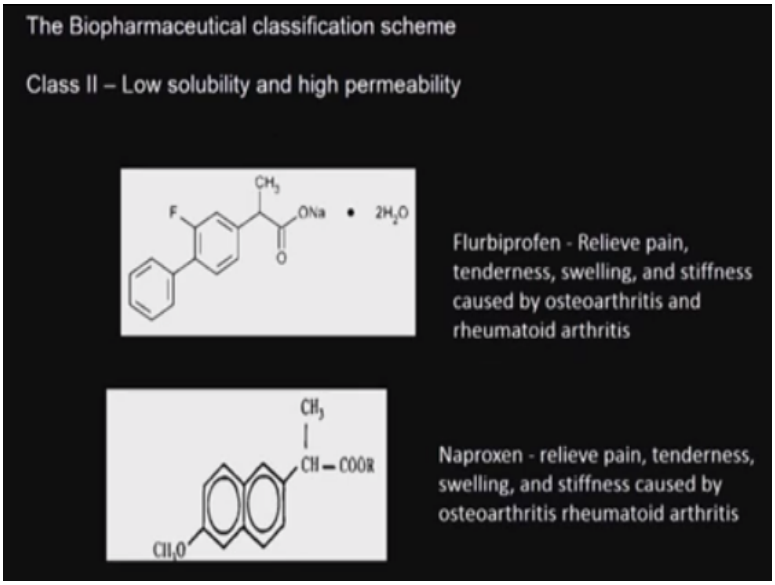

Now let us look at class 2 type of drugs, low solubility highly permeable, that means it is hydrophilicity is less permeability is good, that means it is hydrophobic. Flurbiprofen, just like ibuprofen, relieves pain, tenderness, swelling, stiffness, given for osteoarthritis rheumatoid arthritis. Naproxen relieves pain, tenderness, swelling. So it is got low solubility that means a lot of drug can get excreted from the body because it does not fully dissolve, but permeability there is no point, no problem at all.

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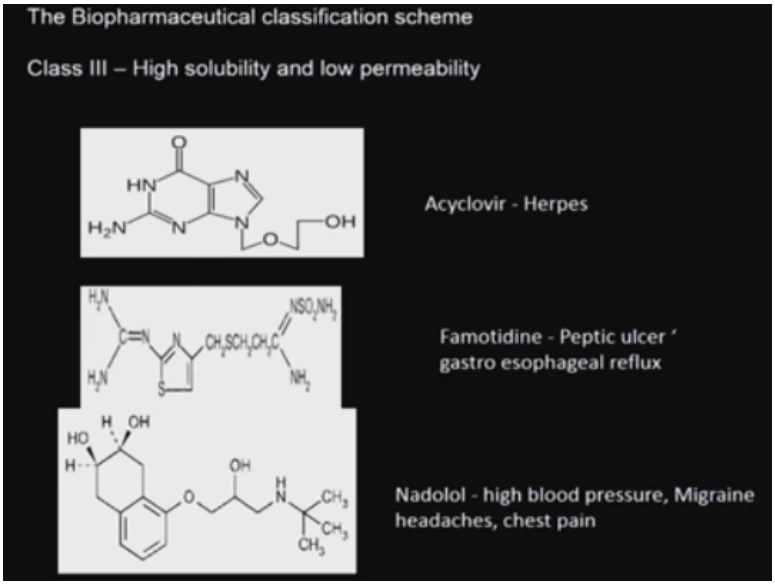

Highly soluble but permeability is low that means it is hydrophilic type of drug. So it does not cross the GI, acyclovir this for herpes so you will see a lot of nitrogens and oxygens. Famotidine, peptic ulcer, gastro esophageal reflux that means acids come out through the esophagus, look at this lot of nitrogen so it is quite hydrophilic. Nadolol for high blood pressure, migraine, headaches, chest pain and so on, again it is got a lot of oxygens.

So high solubility it does not permeate through that so obviously we need some carrier to take it inside the body. Whereas in this class 2 solubility is low and so we can make salts in fact they have made salts from this. They are making salts of this but still solubility is low. So we may need to increase that, so that it dissolves better. Here solubility is good permeability is poor, so we need some carrier type of system to carry it across the GI.

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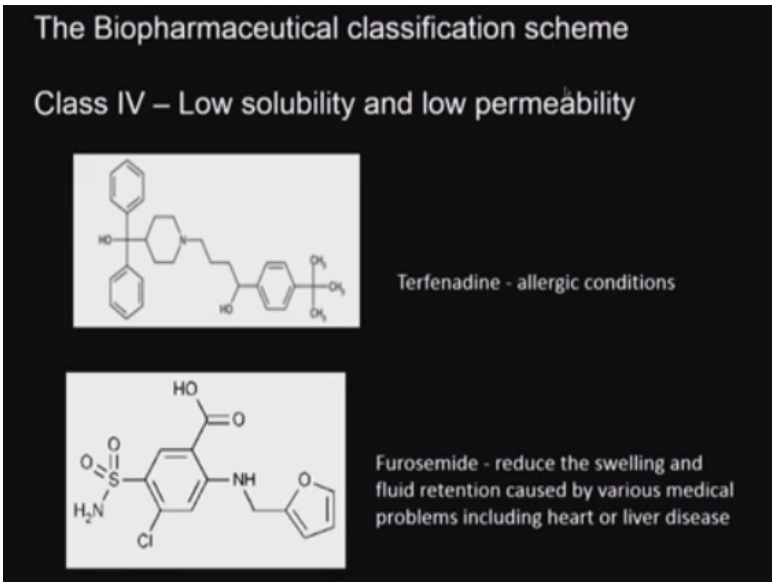

Next one low solubility low permeability. Everything is bad it does not dissolve properly or nicely in the GI at the same time permeability is also very poor. Terfenadine is for allergic, Furosemide reduce the swelling, fluid retention caused by various medical problems. So these drugs obviously have serious problem. If these drugs are given in large doses, you can have toxicities also. So there has to be some structural modifications to these drugs to improve their solubility as well as permeability.

Solubility we can improve easily making salts out of this drug, so that or putting in OH type of group, acidic groups, but permeability may go down. If you want improve permeability we block OH or NH with CH3 that means make it more hydrophobic. So these are the 4 different types of classifications. It is called biopharmaceutical classifications, high soluble high permeable, low soluble high permeable, high soluble low permeable, and low soluble and low permeable.

So for each of these drugs we may require different strategies for improving either the solubility or the permeability. So we will continue further on the bioavailability and ADME. Thank you very much for your time.