Computer Aided Drug Design
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Lecture - 39
Pharmacokinetics/Pharmacodynamics

Hello everyone, welcome to the course on Computer aided drug design. Today, we are going to talk about something new, it is called pharmacokinetics and pharmacodynamics PK PD, this is very, very important, because as soon as the drug enters the body it undergoes so many changes it gets excreted and so on okay, so those aspects are called pharmacokinetics. And the drug acts on the target, drug acts on a bacteria or a cell line that is called the pharmacodynamics.

So how these things happened, can we model this pharmacokinetics and pharmacodynamics is what we are going to talk about in the course of next 2 lectures okay.

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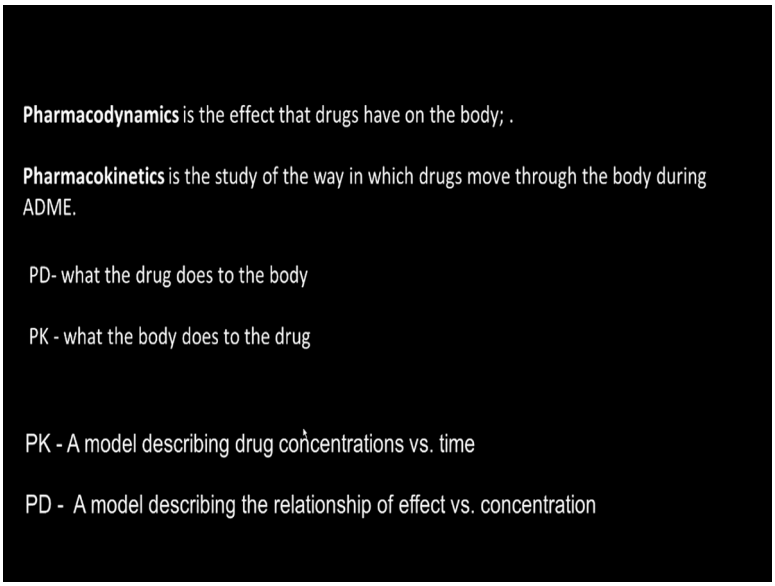

What is this pharmacokinetics and pharmacodynamics? Pharmacodynamics is the effect of that drugs has on the body okay; pharmacodynamics is the effect that drugs have on the body. Whereas pharmacokinetics is the study the way in which drugs move through the body during ADME, because as soon as it get absorbed into the bloodstream, there is a distribution, metabolism, excretion, drugs get eliminated.

So the concentration may go up initially, and then if they start coming down so that is called pharmacokinetics. Now that drug acts inside the body maybe an antibacterial, antibiotic tries to kill bacteria, tries to kill the cancer cell if it is an anticancer drug, so that aspect is called pharmacodynamics. So pharmacokinetics is very important because it tells you what is happening to the drug because of the ADME that is happening in the body okay.

So pharmacodynamics what the drug does to the body, pharmacokinetics what the body does to the drug okay, so both are very, very important and we need to know how to mathematically model all these phenomena. So pharmacokinetics a model describing drugs concentration versus time okay, so the drug concentration changes as a function of time in the plasma.

Then the pharmacodynamics what is the relationship of this effect of this concentration if I put more concentration inside the body will I get better effect or if I have less concentration and I get less effect okay that is pharmacodynamics. So generally in vitro in the lab we will not be able to measure PK, because ADME comes into the picture, but when we do an animal study animal model immediately you come to understand how that drug gets absorbed and then excreted metabolized and so on actually okay.

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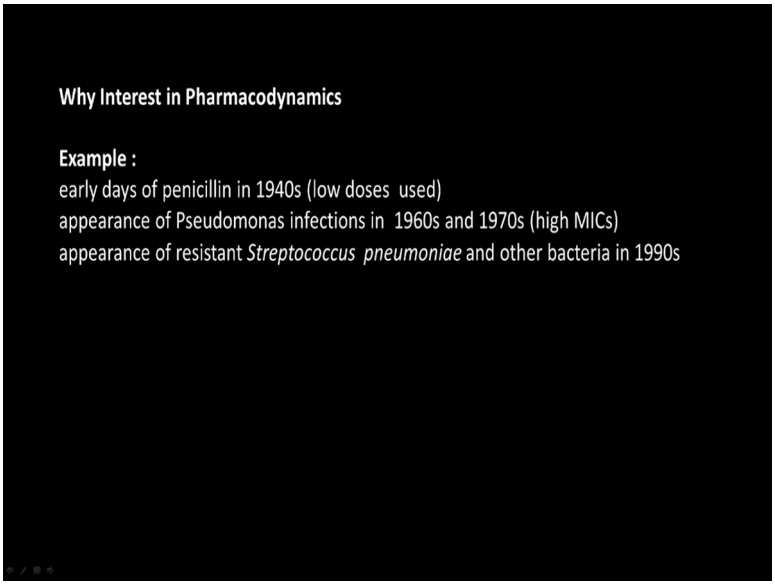

Why there is an interest? This is very, very important because early days of penicillin that is in 40s low dosage were used. But then there were bacteria called pseudomonas which caused infection in 60s and 70s, so that had higher minimum inhibitory concentration okay, so they

had to use higher doses. And then you must have read about resistant strains, so a lot of streptococcus resistant strain started coming in 90s.

So they have to increase the concentration of the drug to kill them okay. So it is not that we all the time use the same concentration, that is why there is an interest in the pharmacodynamics.

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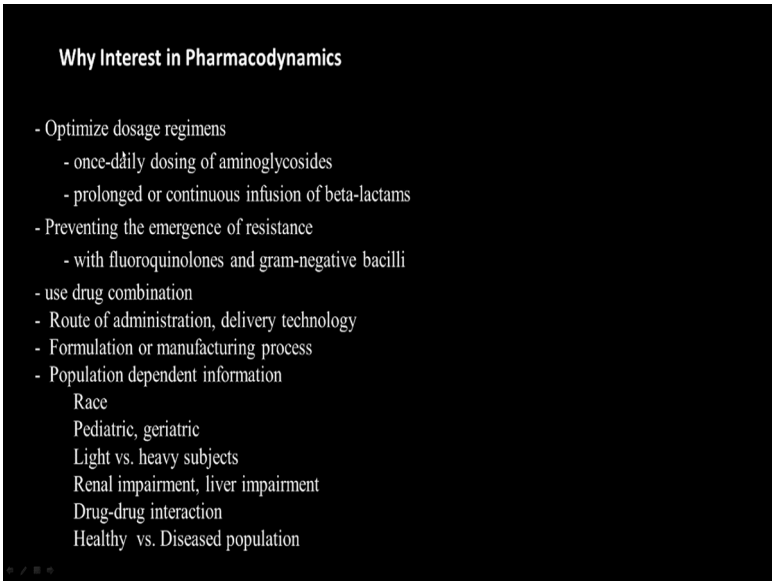

By understanding the pharmacodynamics, we can optimize the dosage regimes once daily dosing of aminoglycoside, prolonged or continuous infusion of beta lactam antibiotics. Preventing emergence of resistance, so use fluoroquinolones and gram-negative bacteria, sometimes you use drug combination. Nowadays, drugs are given in combination, a broad spectrum plus a very specific drug for resistant strains like that you know drugs which will block their flux pumps and then antibiotic.

Route of Administration, should I give the drug orally or through intravenous, so you can understand the delivery technology. Formulations or manufacturing process. And of course this pharmacodynamics is very, very, very population dependent information: race okay, drugs I mean act differently on the say Asian as against the Caucasians okay or the Chinese. Pediatric babies as against old persons.

Light versus heavy subjects okay, if somebody is obese drug may. Renal impairment, the drug could cause problems both in renal and liver region. Drug-drug interaction could be happening, I mean we taking a drug for a blood thinning and the cardiovascular BP lowering

drugs, so there could be an interaction between the 2 drugs. Healthy versus diseased population, so a healthy person the drug may act differently as against the person who is diseased the drug may act differently.

So in order to understand all these we need to know the pharmacodynamics okay.

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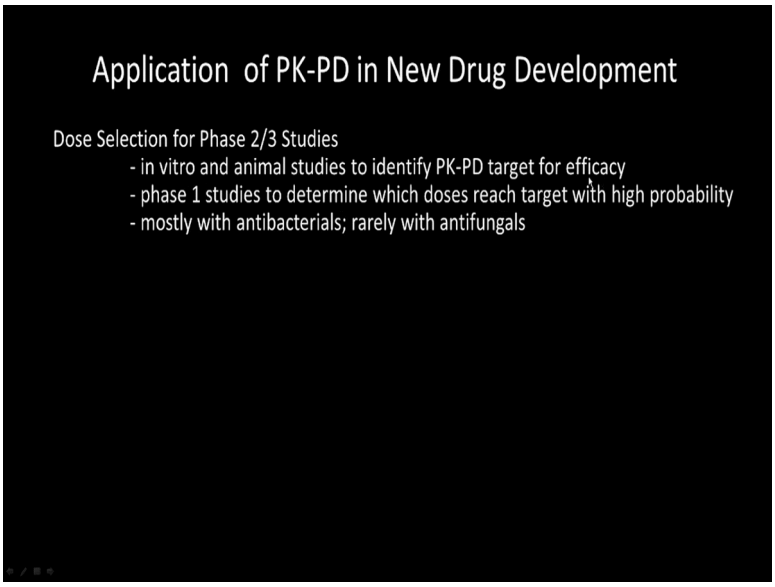

Now, why is it important? Again in new drug development, we need to decide on dose selection for phase 2 and 3 studies. So we need to decide how much the drug has to be given for when you are doing a phase 2 trials, clinical trials and phase 3 clinical trials, as you know phase 2 clinical trials are getting a relationship between dose response relationship, whereas phase 3 is looking at slightly long term effects of that okay.

So we need to know how much dose to be given, so in vitro animal studies to identify PK PD target for efficacy, phase 1studies to determine which dose react reach the target with high probability mostly with antibacterial, but rarely with antifungal. So we need to for all these reasons we need to know the PK PD okay. PK that is pharmacokinetics we have to drug labelling is very, very important which is also approved by FDA, which is also part of the clinical trials.

So I need to know well about that pharmacokinetics in the drug, especially for additional negotiations, need information for prescribing doctors and pharmacists.

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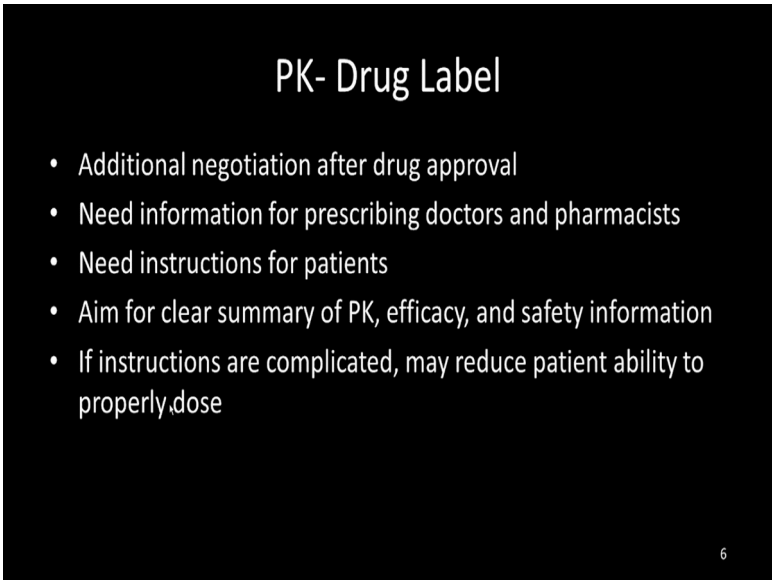

The doctor says take the drug every 4 hours, take drug every 6 hours, so that depends on the PK, that drug gets eliminated very fast, then maybe the patient has to take quite often, the drug remains the body longer maybe not so. If the drug maximum concentration does not reach, the minimum inhibitory concentration then obviously drug prescription is wrong, we may have to give higher dosage.

I need instructions for patient, the patients have to be told okay. So PK efficacy safety information all these is important, if instructions are complicated it may reduce the patient's ability to properly dose okay. If you tell the patient very complicated information or advise the patient may stop taking the drug okay.

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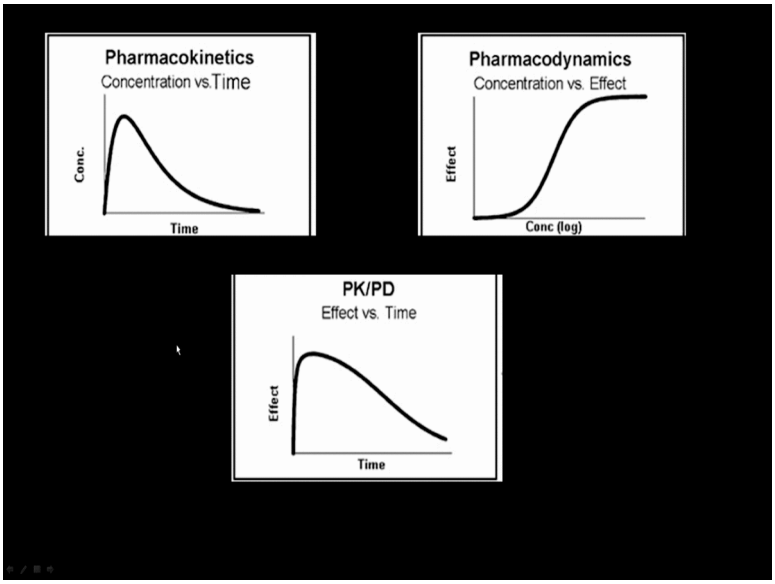

So generally, if you look at a drug we take an oral drug okay, so in the plasma the drug gets absorbed in the gi, so the concentration keeps increasing, increasing, increasing reaches a maximum okay, then it starts decreasing, decreasing because of elimination, metabolism, so many factors as a function of time. So this time could be few hours okay much longer also, now because of this the pharmacodynamics is as the concentration is increased the effect is also fade them out.

So if I have very low concentration of an antibiotic, then number of colonies bacteria killed will be low and so on until it reaches 100% killing okay, this is the pharmacodynamics. So if you combine both you may have this type of relationship as a function of time, so please note as a function of time, the effect may reach maximum but it will start going down because the drug gets eliminated as a function of time, because of elimination and because of metabolism and so on.

So the effects may be felt early very high effect, and then later on starts going down so this time could be different, 2 hours, 4 hours, 6 hours, 8 hours. So if I have a headache pill immediately you feel the effect within 1 hour, whereas if you have an antibiotic or something it may take 2 to 3 hours, whereas if you take other drug it may take 4, 5 hours. So these effect which you feel and then which goes down as a function of time is a combination of both these graphs okay.

So we need to understand the PK and PD properly in order to do lot of planning okay.

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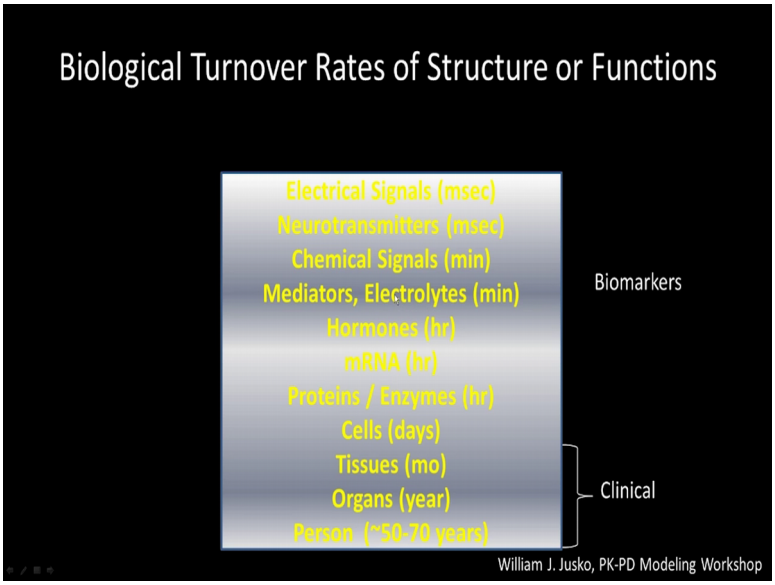

So if you look at biological turnover rates okay for person lives for say 50 to 70 years okay, electrical signal is happened in milliseconds electrical signals is inside the body okay, neuronal muscular neurotransmitters milliseconds, chemical signals like biochemical signals okay it takes minutes. Mediators, electrolytes, Sodium, Potassium again its minutes. Hormonal changes at the body hours. mRNA changes hours.

Proteins, enzymes hours. Cells living cells, dying cell again getting regenerated in days. Tissue, it regeneration mouths. Organ years. So you see the turnover rates or the time scale can change from milliseconds to even years, so organ rejuvenation okay, organ turnover could be years, whereas electrical signal, neurotransmitter signals are in terms of milliseconds. So PK PD is not so simple sometimes PD effects may be it felt after many days or after many months.

Whereas the pharmacokinetics could be in hours okay, so it is very complicated, as you can see from this and this, this I taken from this particular reference actually okay. So that is very important point to note. Here, when we say time regeneration of some tissues take days, whereas drug can get eliminated and metabolized in hours okay. So the effect could be quite different actually okay.

So these are seen chemically, these are seen as a biomarker, biochemically which we can use various tools to determine, whereas this doctor can see through the naked eyes or through certain microscopic measurements okay.

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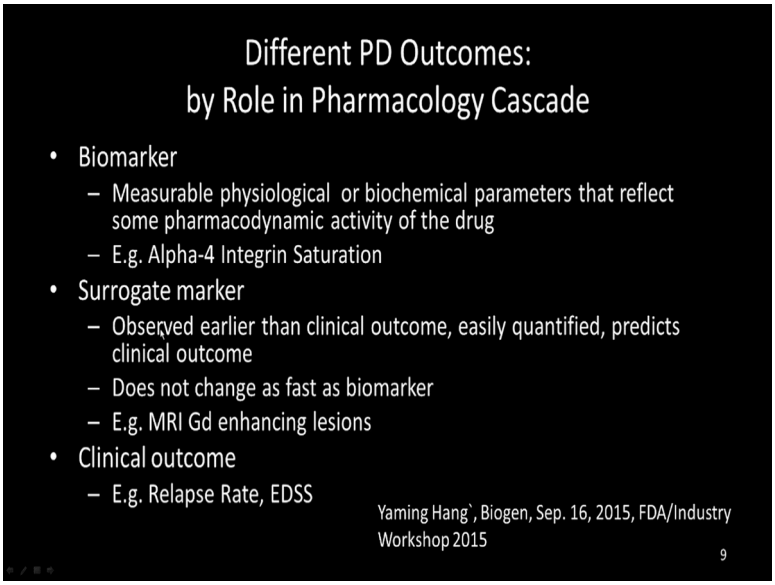

Different PD outcomes by role in Pharmacology, biomarkers we can measure physiological or biochemical parameters that reflect some pharmacodynamic activity of the drug. So we can look at alpha-4 integrin saturation. We can also look at surrogate marker, not the same but we can look at something else because which may be changing because of the main marker. Observed earlier than clinical outcome, easily quantifiable, predicts clinical outcome.

Does not change as fast as biomarker okay, surrogate marker MRI Gd enhancing lesions. Clinical outcomes okay, this is going to take much longer, relapse time okay because of my drug the relapse time of the infection gets longer. But this is going to be in days or weeks okay, so this is much lower. Whereas these could be in terms of minutes and hours, it could be in terms of hours, and this could be in terms of days and weeks okay.

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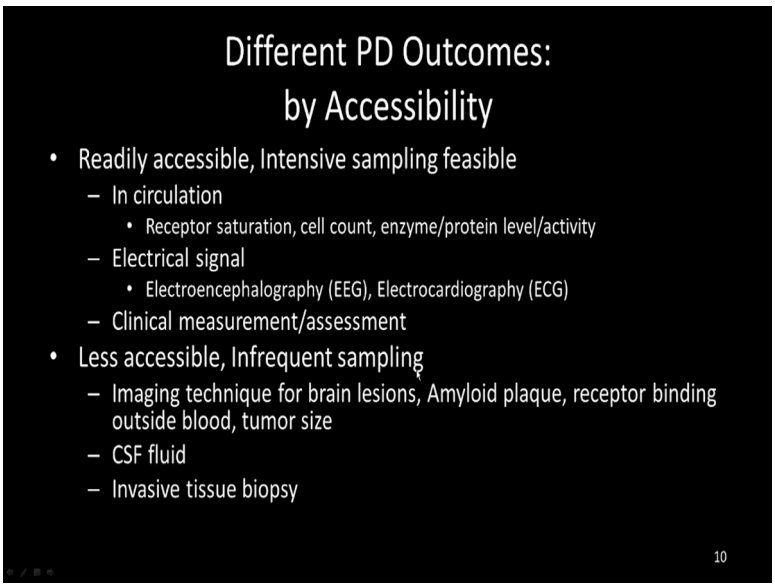

Then we have more readily accessible intensive sampling feasible okay, receptor saturation, we can do cell count, we can do enzyme protein level activity. We can look at electrical signals like EEG, ECG, EME. Clinical measurement, biochemical measurements okay, this is also possible, which are easily measurable not difficult. Of course there are things like less accessible, infrequent sampling: imaging techniques for brain lesion.

We cannot keep on doing MRI of the brain every hour or something, we might be able to do it only once in several months. Amyloid plaque okay, receptor binding outside blood. Tumor size we cannot measure tumor size everyday okay, because the tools are difficult make a once in a month or 2. Invasive tissue biopsy, again we cannot do the invasive tissue biopsy everyday right. CSF fluid okay, cerebrospinal fluid we cannot take it every day right.

We cannot take it even every week, you may be able to take it once in a few months that is all okay. Because it is quite an annual the type of invasive procedure.

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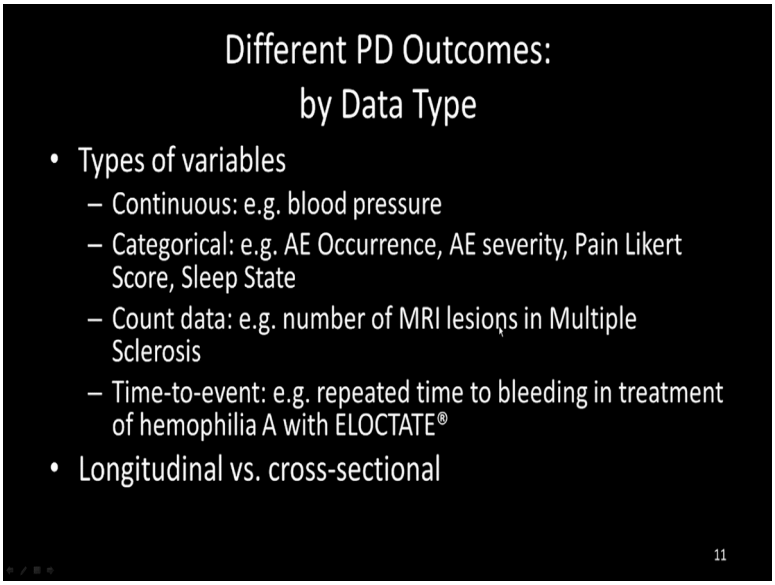

Types of variable: continuous blood pressure we can measure continuously of course, we can look at AE occurrence, AE severity, pain likert score, sleep state okay. We can look at number of MRI lesions, so these are all more like number continuous, these are numbers, this is continuous. Or we can look at time-to-event, repeated time to bleeding in treatment of hemophilia A with some drug okay.

We can look at even longitudinal versus cross sectional, if you are looking at that some okay tumors, we can look at the longitudinal and cross sectional and decide what is the effect of a drug on that or effect of certain procedure or treatment.

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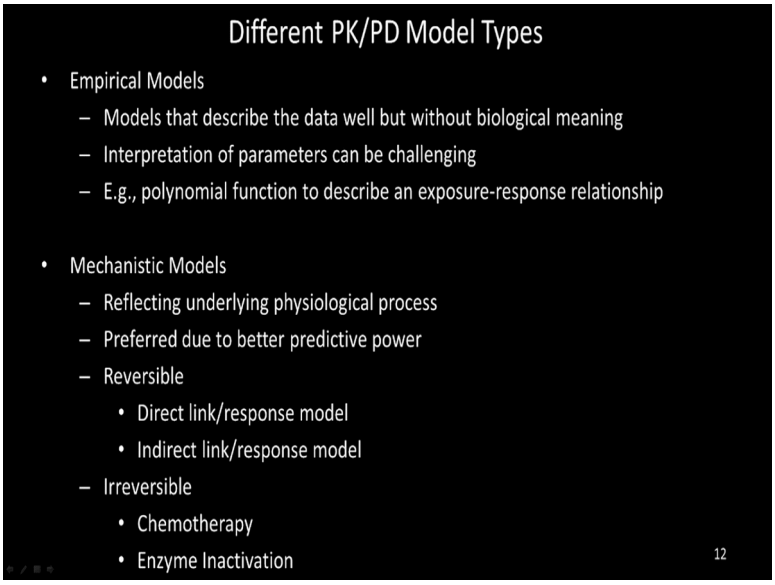

Of course there are a lot of mathematical models that are coming up late, because we need to predict the future events if you have a mathematical model. There are different types of approaches we will look at some of them. Empirical models, models that describe the data well but without biological meaning okay, like the statistical parameter fitting type of model. Interpretation of parameters can be challenging right.

So we can say y=Ax+b, so x is the drug concentration, y is the number of life cells, so as x changes y changes, but A and B are fitting parameters, we cannot say mechanistically what it means okay, so that is all empirical models, but they are also useful because we can try to predict the future effect of other concentrations on that. Mechanistic model okay, so we can incorporate the underlying physiological process, that is going to be tough okay.

It is got better productive power, we will be able to understand some physiological mechanism involved, direct link response model, indirect link response model that is in reversible case. Irreversible like chemotherapy, enzyme inactivation, so we can have mechanistic model in such situations also okay. Deriving mechanistic model are a bit tough, because I need to know the mechanism of action of a drug leading to a particular effect and there could be lot of parameters which you might not know okay.

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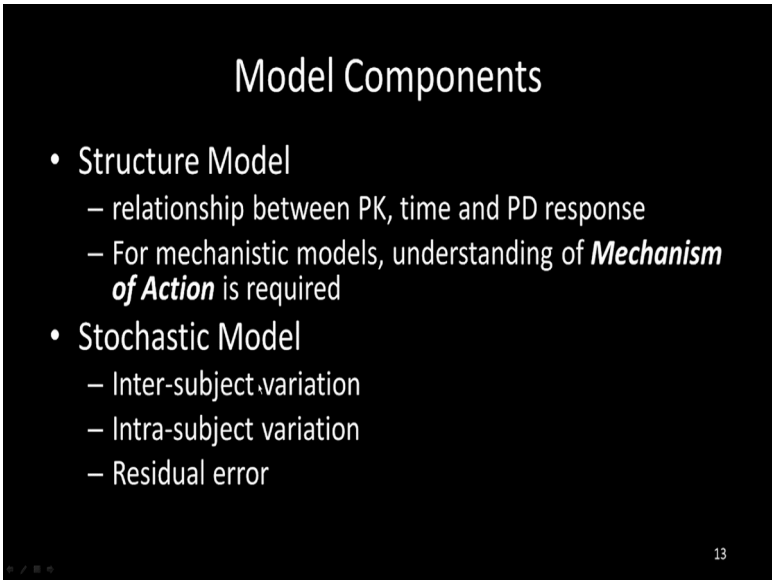

We also have structured model, stochastic model okay. So we can have structure relationship between pharmacokinetics, time and PD response. For mechanistic model I need to have an understanding of the mechanism of action I need to know. Stochastic model inter-subject variation, we need to put intra-subject variation, we need to put errors, because if I take a 100 population there could be variation between the people within that sample group population.

But if I take a 2 or 3 different populations, I take South Indians, I take North Indians, Eastern part of India that is the intra-subject, there could be variations between them. And then I should also know idea about the residual error that is involved okay, so that is called stochastic model it is a very statistical approach we use in this type of a model okay.

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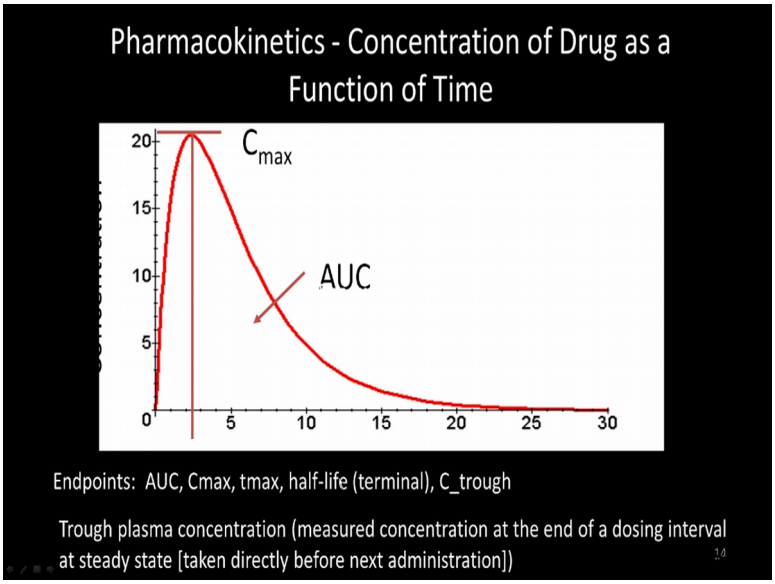

So as I showed you before if you are looking at the concentration of a drug in the body, so it goes up reaches a max and then it starts coming down as a function of time, so this x-axis could be hours, y-axis could be milligrams microgram okay per liter per ml and so on actually okay, this is called the area under the curve AUC, Cmax is this concentration okay, tmax is the time at which this happens half-life concentration of the time.

It takes to eliminate half of this material okay, so all these are of course there is one more parameter called C_trough, this is trough plasma concentration measured concentration at the end of dosing interval at steady state okay taking directly before next administration, that is this is the trough concentration into the dosing interval. So all these are endpoints we can measure easily okay, when we keep taking samples from a subjective patient or volunteer or an animal and we can measure all these okay.

So we can get the pharmacokinetics parameters okay, these parameters are very useful in our modeling strategies, and later on we will see it.

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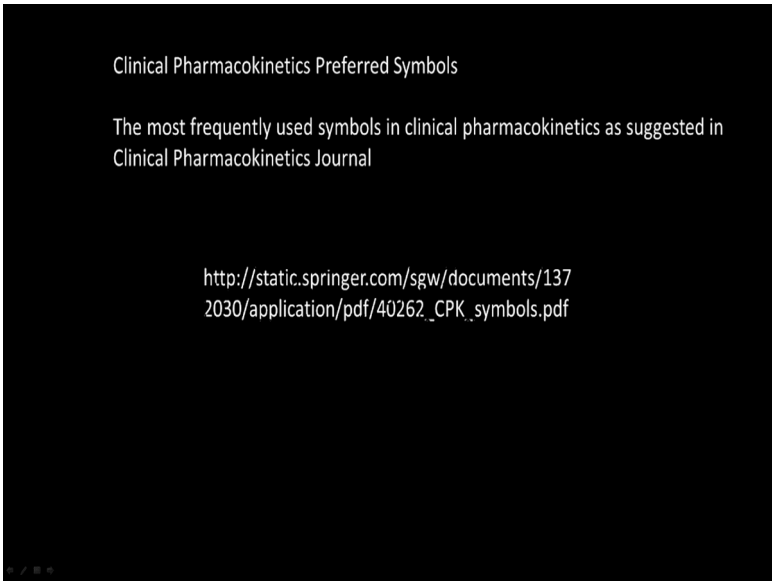

There are lot of symbols that are used in the clinical pharmacokinetics, these are most frequently used symbols in clinical pharmacokinetics as suggested by clinical pharmacokinetics journal. This PDF is very, very useful, you can download that because there are standard symbols which are used, and it is good for all of us to use the same standard symbols in pharmacokinetic speaking okay, so we will also use okay.

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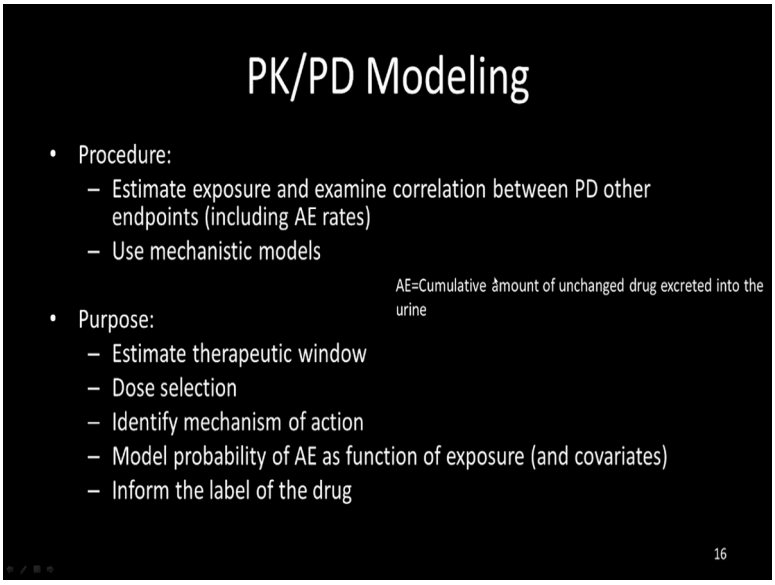

PK/PD modeling estimate exposure and examine correlation between PD and other end points, AE is cumulative amount of unchanged drug excreted into the urine okay. So we give certain concentration goes to the plasma, and then it gets eliminated not metabolized but eliminated of course there will be metabolism also, but AE is the cumulative amount of unchanged drug excreted into the urine.

This modeling is very important because we can estimate therapeutic window okay, like I showed you here, so after sometime concentration goes down, so the effective concentration maybe much higher here okay here, so I need to again give another dose to the patient. So that the drug has an effect, so I need to know therapeutic window dose selection okay, how much should be the concentration of the drug to be given orally or IV.

Identify mechanism of action, we can understand elimination happens very fast, if I know the AE I can say where elimination happens fast, if AE is very low than I know metabolism happens. So model probability of AE is a function of exposure, and inform the label of the drug, so we can inform the label of the drug what is happening to the drug? As it gets eliminated from the body.

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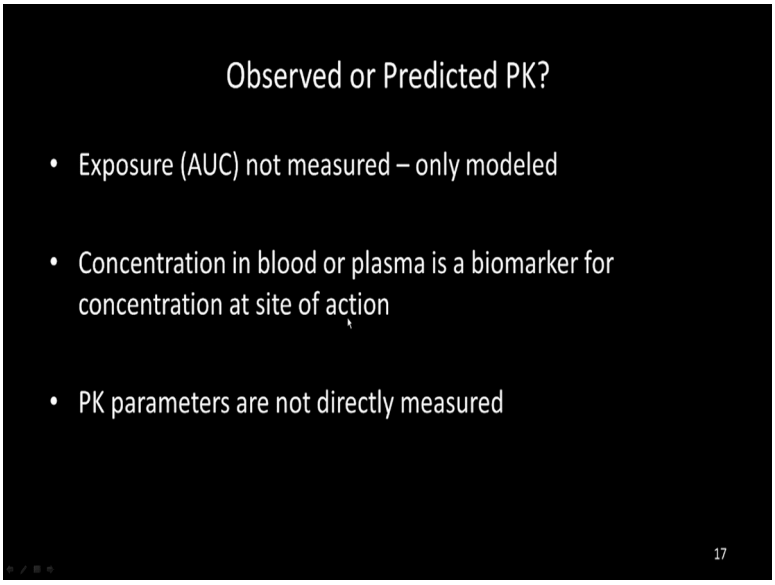

Exposure AUC not measured only modeled, so we can use it for predicting PK. Concentration in blood plasma is a biomarker for concentration at the site of action, that is another important point you need to know. You assume that at the site of action whatever be the concentration is same as what is in the plasma. PK parameters are not directly measured, but we do measure it directly we will go through how to estimate all those things okay.

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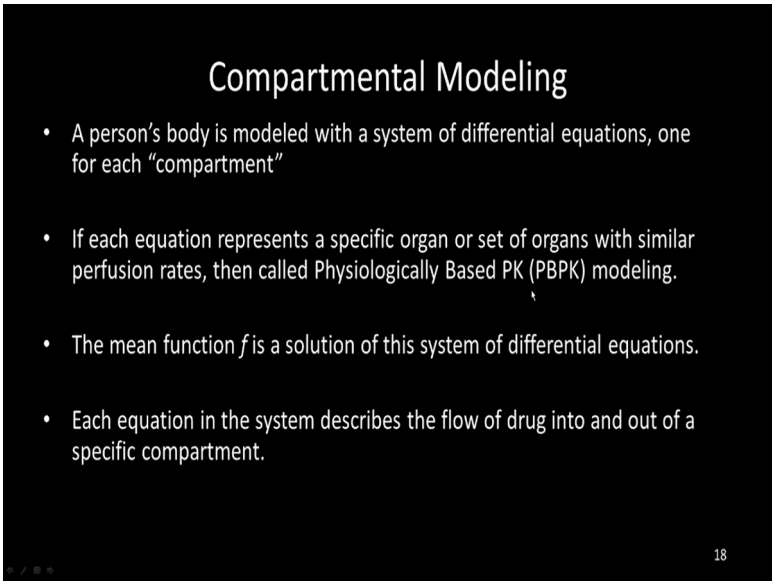

Okay, a person's body is modeled with the system of differential equations one for each compartment okay, so for the blood plasma region we call it one big compartment or big bucket like, the issues can be another compartment organ specific organs could be another bucket and so on. So for each, then there will be an equation representing each organ or set of organs with similar perfusion rates okay, then called physiological based PK modelling okay.

So we can have different compartments for organs of interest or we can have one compartment coupling many organs based on that perfusion rates, then we will say drug is going in, drug is coming out and so on actually. So we will have set of differential equations, and then we can solve the differential equation. So each equation system describes the flow of drug into and out of a specific compartment okay, into and out okay.

So we can have different amounts flows going in it is a liver, different amounts flows going into the say tumor and so on actually. And then you try to solve all these differential equations as a function of time, so we will be able to predict concentration changes inside the plasma as a function of time okay.

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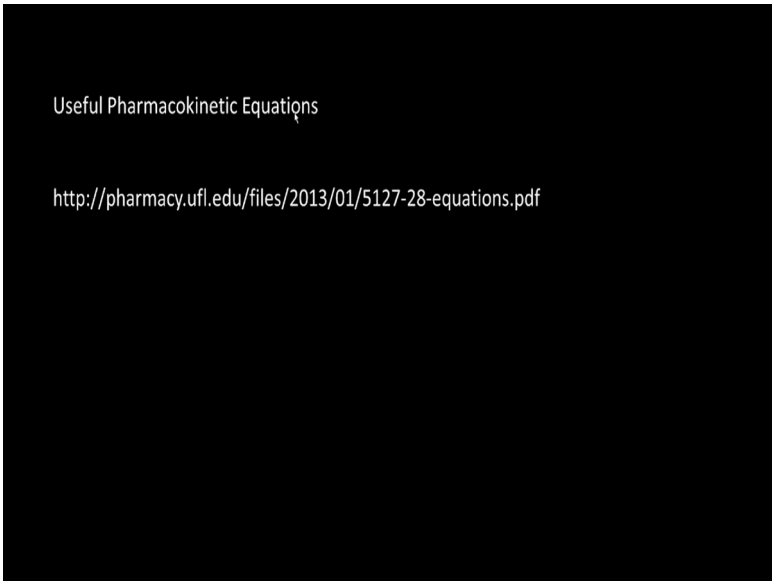

There are again please look at this particular PDF, a lot of pharmacokinetic equations given in the PDF, I am going to adapt some of them from this reference, but if you want to go more in detail you can look into this particular video from this website okay.

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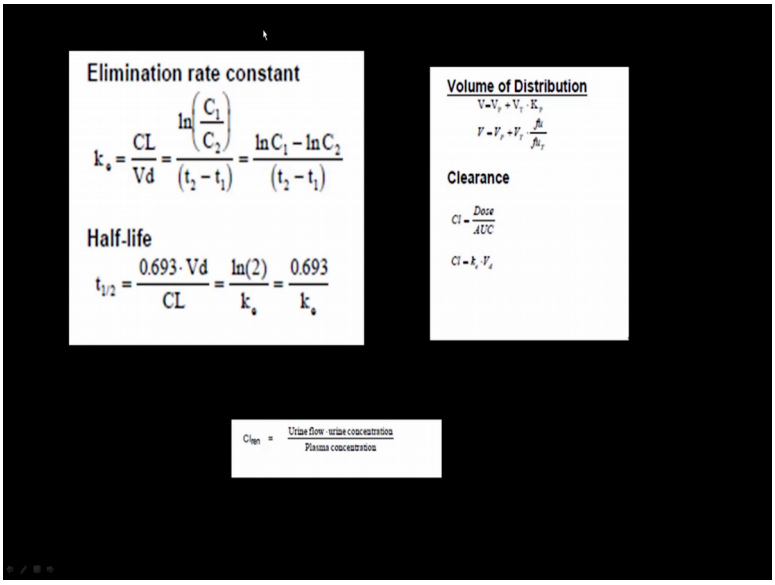

So the elimination rate constant ke is given by CL clearance/volume of distribution okay, and clearance is given by logarithm of C1/C2/t2-t1, so we have the CL clearance/Vd clearance/volume is given by logarithm of C1/C2/t2-t1 and that is logarithm of C1-C2/t2-t1 okay. So how did this equation come about, because as you know elimination happens exponentially okay, so because that is why we have this logarithm.

Half-life, that means what is the time drug concentration reaches 1/2, 0.693 Vd volume of distribution/clearance or 0.693/k elimination that is rate constant. So we will look at them later also this half-life and ke and all that actually okay. Volume of distribution we have many terms here okay, V-Vp+Vr Kp okay clearance is dose/AUC that is area under the curve okay, so area under the curve we can measure once we get the concentration at different time points.

We can integrate that okay. Cl renal clearance renal is urine flow into urine flow*urine concentration/plasma concentration, this is called Cl renal okay clearance in the renal region, like you have urine flow in concentration, you have plasma concentration and renal okay.

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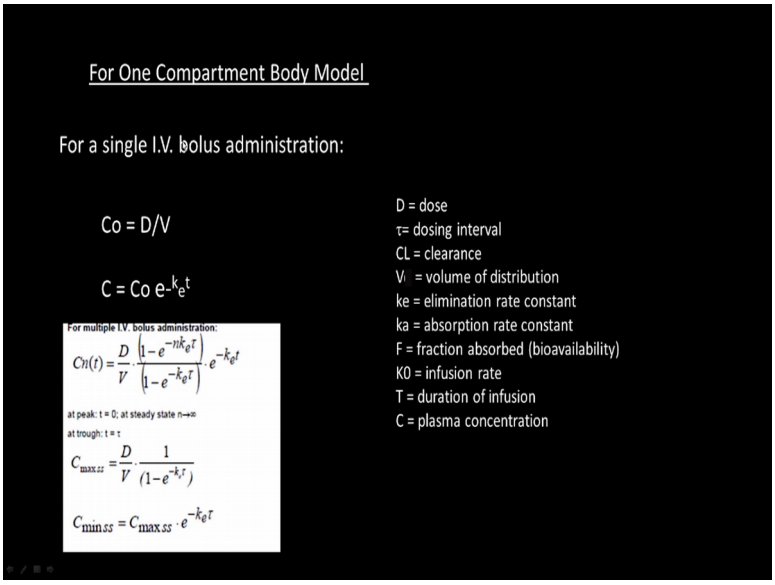

So let us look at the one compartment model, this is the entire body is taken as one single compartment.

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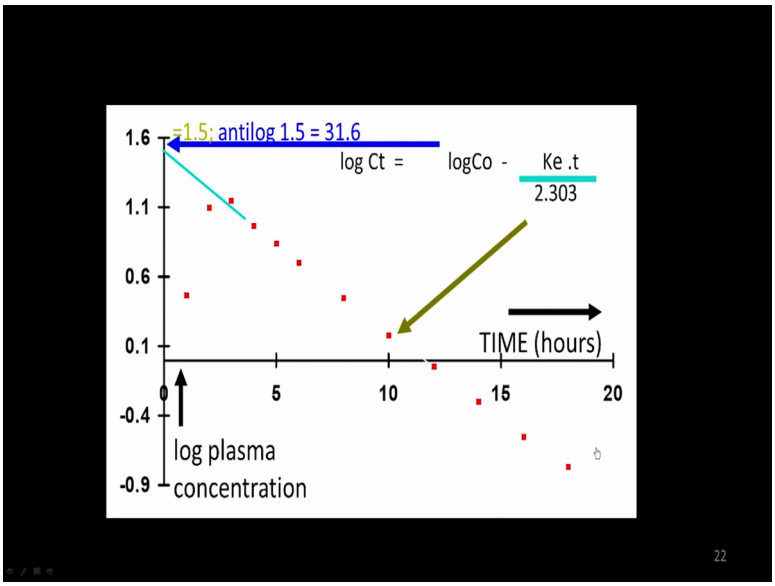

We can have the dosing both okay for a single IV bolus administration, that means intravenous you give the drug in one shot okay, the whole drugs you do not take some time delta t time for injecting the entire drug into the okay in the plasma okay. So we have C0=D/V, D is the dose we give, V is the volume, C=C0 e-ke/t, that means this is the first order relationship. The concentration as it changes they follows a first order relationship which gets eliminated as a function of time.

So this is taken as first order that is why we have C=C0 e-ke/t, so your C0 could be here, and this gets eliminated as a function of time, so we take it as a first order here actually okay. So

for multiple IV bolus administration, that means we give intravenous many times but it is a bolus, bolus means it is given in one shot okay, so the equation is slightly modified, we have n is the number of administration okay.

Cmax that is the maximum concentration is also given by this relationship D/V okay, V is your volume of distribution 1-e-n ke tau and so on actually okay, this is for a one compartment model, where we talk about single IV bolus administration or multiple bolus administration. Now look at this particular graph, as I mentioned the concentration in the plasma goes up and then it starts going down okay.

So this portion we okay this portion of course this happens if it is an oral dosage, otherwise if it is injected in one shot concentration reaches max immediately okay bolus, and then it starts going down, this is for oral administration because of the gi absorption concentration goes up then it falls down. Now this portion can be modeled as a first order relationship C=C0 e- as it is shown here e-ke t, ke is the elimination rate constant okay.

So take logarithm log Ct=log C0-ke t/2.303, why this comes because normally we take ln when we take log then the 2.303 comes in, so if you draw a straight line okay and then take the slope we can get ke/2.303, here t is the time and the here is concentration. And then you extend this line up right up to that okay, then you take antilog then that becomes the C0, this is how you measure C0 and ke for the elimination side.

You give a oral dose or if you give oral dose you will have like this, if it is a direct IV bolus dose you will not have this portion, we will have max concentration and so it will fall down. So you take the slope, the slope is equal to negative slope of course, slope will be ke/2.303, so you extend it like this and take a antilog that will give you a C0. So generally animal studies performed, and from if the drug is given orally they get a graph like this.

If you take samples from the blood at different time points, and then from the slope of this portion they assume they get this ke/2.303 and by extending this and taking antilog then get the C0 okay. So in a one compartment model it is quite simple, you expect the graph to be like this okay.

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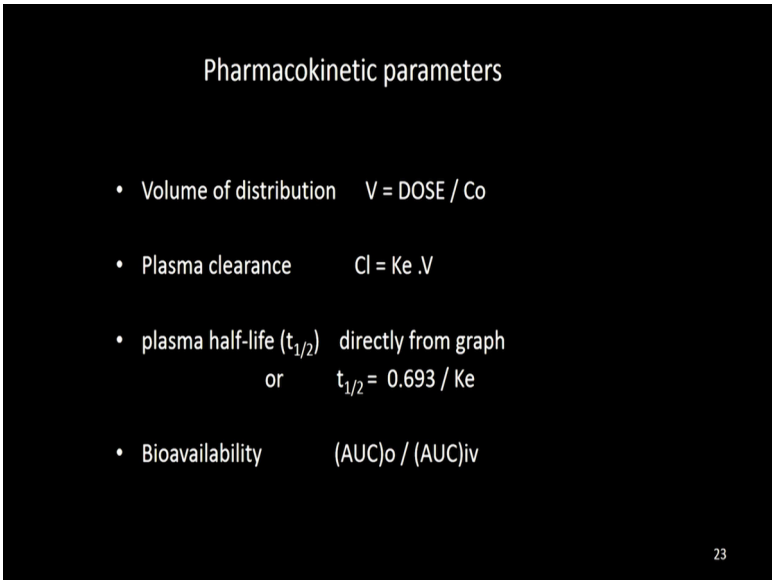

So the volume of distribution in a one compartment model V=dose/C0 okay, C0 is here, dose is the amount of drug you give orally. Plasma clearance=K elimination*V, so from here C0 if you know from the graph, you know how much dose we are given we can get V and then you substitute here, and Ke you can calculate from the slope, then you get clearance. And the plasma half-life is 0.693/Ke okay, so we can put it here we can get half-life.

The bioavailability is AUC when you give it orally/AUC when you give intravenously. So all the important parameters we can get by looking at this type of graph, PK graph that is the concentration of the drug in the plasma as a function of time. Okay, so we will continue more on this topic of PK PD in the next class as well, thank you very much for your time.