Drug Delivery Principles and Engineering
Prof. Rachit Agarwal
Department of BioSystems Science and Engineering
Indian Institute of Science, Bengaluru

Lecture – 02
Pharmacokinetics Cont

So hello, everybody; welcome to the second lecture of the course Drug Delivery Principles and Engineering. In the first lecture, we learned why the drug delivery is important, what are the different modes through which the drugs get distributed in the body. So, some pharmacokinetics is what we learned and we are going to continue further into the pharmacokinetics and introduce some more terms so that throughout this course these terms will be used and you are familiar with these terms and know what these means before we go further into the course.

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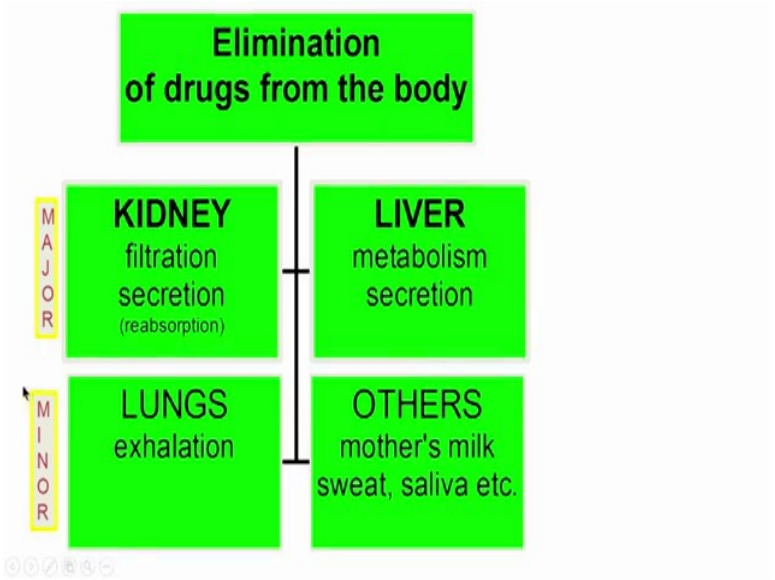

So, today we are going to talk about elimination we are talked about drug distribution previously a bit, this lecture is going to be mostly about elimination. And, so, how are the drugs eliminated from the body. So, there are few major mechanisms and minor mechanisms that are responsible for the clearance of the drug or elimination of the drug. By far the most major mechanism is the through the organ called kidney as you might already be aware of. We secrete a lot of urine through which we clear lots of drugs through our body.

So, the major organ responsible there is kidney which is responsible for filtration, which is responsible for secretion and which is actually also responsible re-absorption which basically means that if you have let us say a molecule that the body may require and it does end up making it is way to the kidney, the kidney will send it back into the circulatory system so that we are not running out of those particular molecules. So, these can be proteins, these can be other important things that the body may need.

So, again as I said by far when we talk about elimination, kidney is the major organ responsible. The next major organ is the liver and again, as we discussed in the previous lecture about first pass metabolism liver is essentially the metabolic organ of the body which basically means it can be lots and lots of enzymes, lots of contact with the drug in the plasma. So, what it does it breaks the molecules down into several individual components which unlike kidney does not directly eliminate from the body.

It will still have to go through the kidney to get eliminated completely from the body, but then let us say if a molecule is broken down into three different smaller fragments, the activity may get lost and so that way the drug itself is eliminated and converted into some other format and it is no longer active. So, that is why it is important to talk about liver when we are talking about elimination. So, these two are the major organs that are responsible and again depending on the drug there might be some other organs as well depending on how the drug is interacting with the body, but in general these two are the major organs.

Then we also have some minor organs that are responsible for elimination and one of them is lungs. So, mostly the elimination of the lung is through exhalation. So, we take in oxygen we are eliminating CO_2 every time we breathe. We are also eliminating some of the water every time you breathe. So, there is some moisture in the air that we are exhaling out. So, if you let us say inject a gas into the lungs or gas into the circulatory system those gases will have to then diffuse through to the lungs to get eliminated from the body.

And, then there are other some very very minor mechanisms that could include sweating. So, we eliminate lots and lots of ions and water, when we are doing some physical activity or when we are sweating. Saliva is another way that we eliminate few of the enzymes as well as some of the drugs and of course, very minor contribution in very many different circumstances is mother's milk and things like that.

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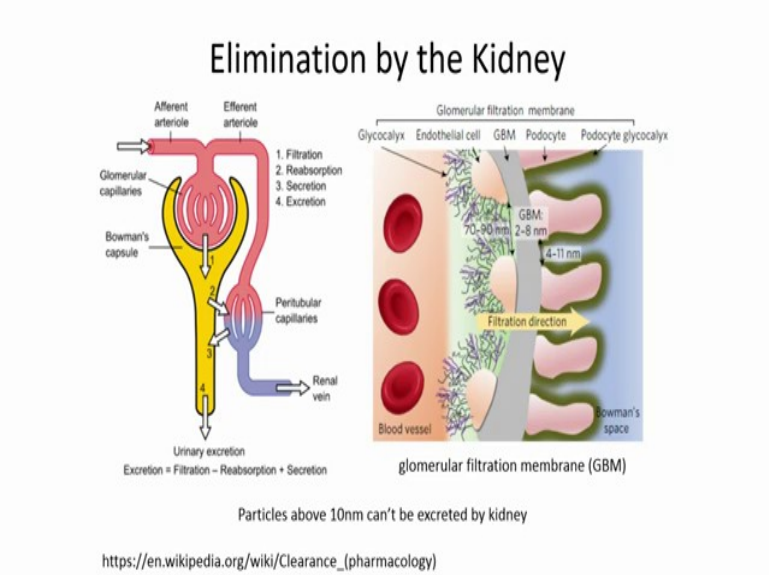

So, let us talk about elimination at the kidney since we said that this is going to be a major organ through which the elimination is going to take place and so, essentially this is kind of a small unit in the kidney it is called Bowman's capsule and what it is in the red, what we are seeing lots and lots of blood vessels very very tiny capillaries glomerular capillaries that interacts with the Bowman's capsule at a very close proximity as you can see here. And, because of this close proximity, there is exchange of fluid, there is exchange of nutrients, there is exchange of drugs at this interface. And, so, the drugs can typically diffuse out from this area into the Bowman's capsule which essentially then goes towards the urine and causes the elimination.

So, this is essentially where all the filtration, all the secretion happens and so, if I really zoom into this mechanism one then and here is a picture on the right which shows it. So, this is a zoomed in capillary taking blood cells through it and also your drug of interest. At the interface you have some endothelial cells which also have their glycocalyx; glycocalyx is nothing, but these proteoglycans, these lots of like glycosylated proteins and that are there. And, they form a very tight mesh network which essentially filters anything above 100 nanometer is not able to pass through these and, but anything lower than that can essentially diffuse and filter out through these glycocalyx network.

Then we have a globular basement membrane through which about up to a maximum of 10 nanometer can pass through and then we have podocytes which are the kidney cells and they

are spaced such that, the act as filters anything below 10 nanometer can pass through and again it depends on the state of the person, what age they are, if they have any disease these gaps may change depending on that, but in general anything below 10 nanometer is typically considered to be cleared by the kidney.

And, so, take away from this is that particles that are above 10 nanometer cannot be excreted by kidney. So, let us say we want to eliminate the kidney excretion, what we would want to do is to make particles that are more than 10 nanometer in size and those particles will then be entrapped and will not be able to pass through the kidney.

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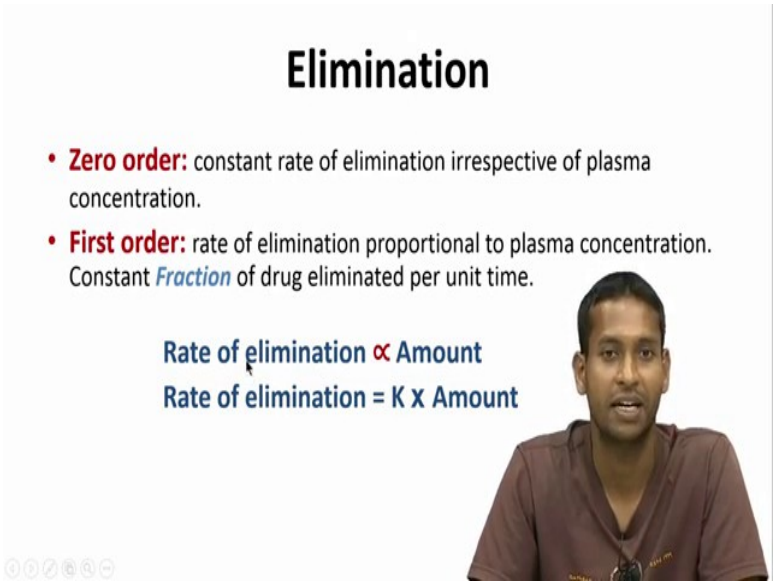

In terms of the actual mathematics of this elimination can be of various different types, one is zero order elimination. So, that means, that there is a constant rate of elimination in the respect of the plasma concentration. So, now, we are talking about that let us say we have a certain plasma concentration c in serum of a drug and we are talking about how fast is going to be eliminated we want to study that.

And, why it is important? It is important because let us say if we want to figure out at what dose we should give it to a patient we need to know first of all at, what dose is the drug therapeutic. Let us say for example, a drug x at 100 mg per ml and takes about 1 day for it to manifest its effect. So, we would like that the drug should be present throughout the body at least 100 mg per ml for 1 day and to know that we need to know that how much drug we

should give so that the levels of the drug should never fall below 100 mg per ml at least for a day.

So, that is why it is very important to know at what rate it is building up as well as eliminating from the body and there are some kinetics that are defined and so zero order is one of them and so, when we say zero order, it essentially means that it is a constant rate of elimination. So, no matter what is the drug concentration in the serum it will eliminate at a constant rate.

Another one is a first order which is typically seen most often than not and what it essentially means is the rate of elimination is proportional to the plasma concentration. So, essentially more drug you have in the body, the faster the drug is going to get eliminated and then as the drug concentration is going to go down the rate of elimination will also go down. So, essentially saying that constant fraction of drug is eliminated per unit time rather than the constant amount.

And, then of course, there can be several other types of kinetics, there can be a second order or third order, but we are not going to go much detail into that. So, if you are talking about first order, it can be mathematically expressed as:

Rate of elimination $\propto$ Amount

And, so, essentially you can take out the proportionality constant and say:

Rate of elimination = K x Amount

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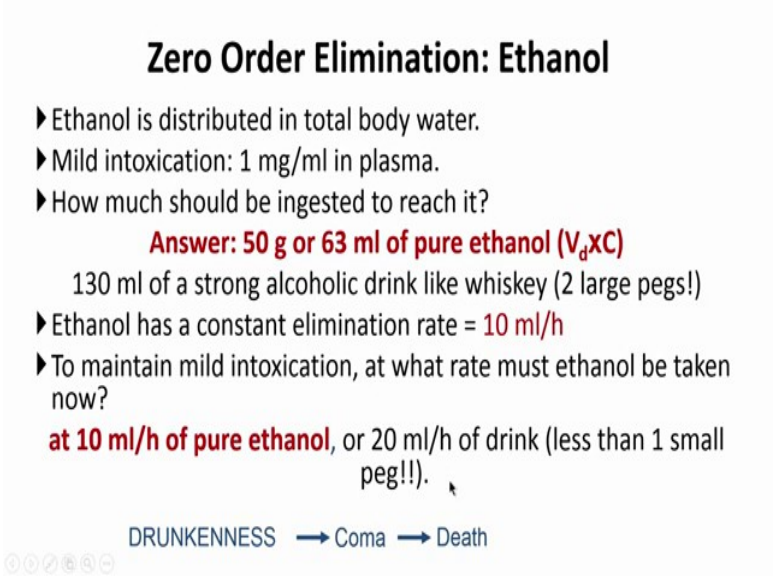

So, that is for the first order and we come back to it. Let us talk about an example and so, in this case we take a very popular example especially among young adults which is a zero-order elimination of ethanol. So, ethanol when we consume it, it is typically distributed in the total body water. So, not only in the plasma, but everywhere in the body wherever the fluid is and we discussed in the last class that typically 80 kg human will have somewhere around 50 liter of total body fluid that will circulate.

So, for a mild intoxication to happen through ethanol we need to have a plasma concentration of 1 mg per ml and when again as I said that ethanol is distributed throughout the total body water. It essentially means that the total concentration of ethanol in the body should be close to about 1 mg per ml in all parts of the body including the plasma. So, how much should be ingested so that we reach that concentration or how much at typically when a person injects or consumes that much does it go to 1 mg per ml?

So, as I said the total body water is about 50 liters and so, we need to consume about 50 grams. So, if we consume about 50 grams we are talking about 1 mg per ml total plasma concentration which is essentially if you consider the density of the ethanol we are be talking about 63 ml of pure ethanol. So, ok. So, let us say a person does consume about 63 ml of pure ethanol, builds of the plasma immediately builds of the plasma concentration to be about 1 mg per ml and then what is the next thing is going to happen?

So, I mean technically if we are talking about strong alcoholic drinks like rums and whiskeys, they have about 40 to 50 percent of ethanol concentration. So, we are really talking about 130 ml of strong alcoholic drink. So, it is not too high of a thing that people do not drink that much. So, it is easily can be build up to that amount. Now, from the studies we know that ethanol has a constant elimination rate. So, as I said zero order elimination rate of about 10 ml per hour. So, regardless of what is the concentration of the ethanol that is present in your serum, it will get eliminated at a constant rate of 10 ml per hour.

So, how much should a person be drinking to be able to maintain a mild intoxication which is at 1 mg per ml, if we know that this is the elimination rate? So, I will I will give you guys a couple of moments to figure this out. So, remember we are saying that the elimination is 10 ml per hour and mild intoxication rate is 1 mg per ml so, in the plasma. So, how much should the person be drinking so as to maintain this 1 mg per ml concentration in the plasma? Ok. So, it is very simple answer to this essentially we should be drinking at a rate which is equal to the elimination rate. So, if we keep drinking at 10 ml per hour that would maintain a concentration of 1 mg per ml and that is fairly easy because it is a zero order elimination.

So, of course, the answer is that we have to drink at the rate of 10 ml per hour of pure ethanol which again; that means, 20 ml per hour of a strong drink which is about 50 percent in concentration with the ethanol and so, that is really not a whole lot we are talking about less than one small peg. So, it is very easy to maintain this intoxication level and in fact, it is very easy to go above this if you continue to drink irresponsibly. So, essentially word of caution, if you drink too much the drunkenness can lead to coma and eventually to death. So, drink responsibly, but that is a very classic example of a zero order elimination with ethanol.

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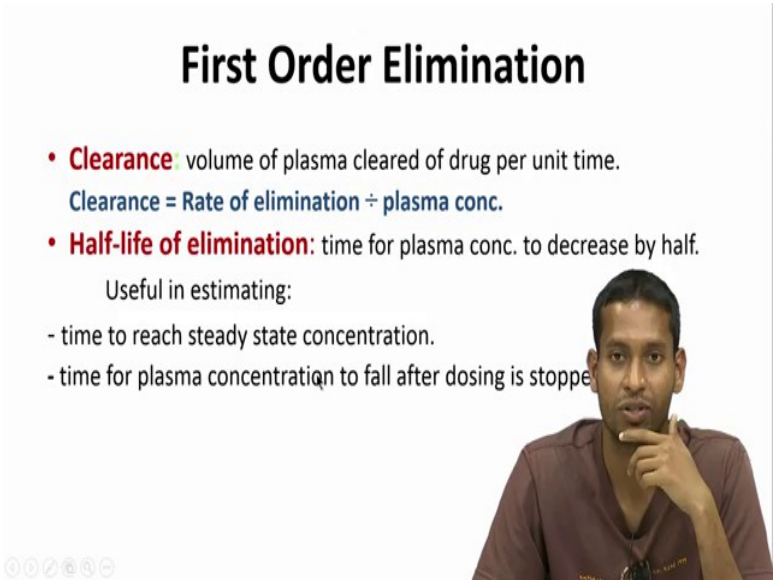

Let us talk about first order elimination. So, here we are going to define another term called clearance. So, what is clearance? Clearance is the volume of the plasma cleared of drug per unit time. So, essentially clearance can be expressed as:

Clearance = Rate of elimination ÷ plasma conc.

then another term that were going to define is half life of elimination and so, that is very very widely used in drug delivery fields. And, what it essentially means is, the time it takes for the plasma concentration to decrease by half. So, if I have 1 mg per ml how long would it take for a normal body to reduce, it down to 0.5 mg per ml.

And, so, again this helps in telling us the time to reach a steady state concentration when you administer a drug as well as time for plasma concentration to fall after dosing is stopped.

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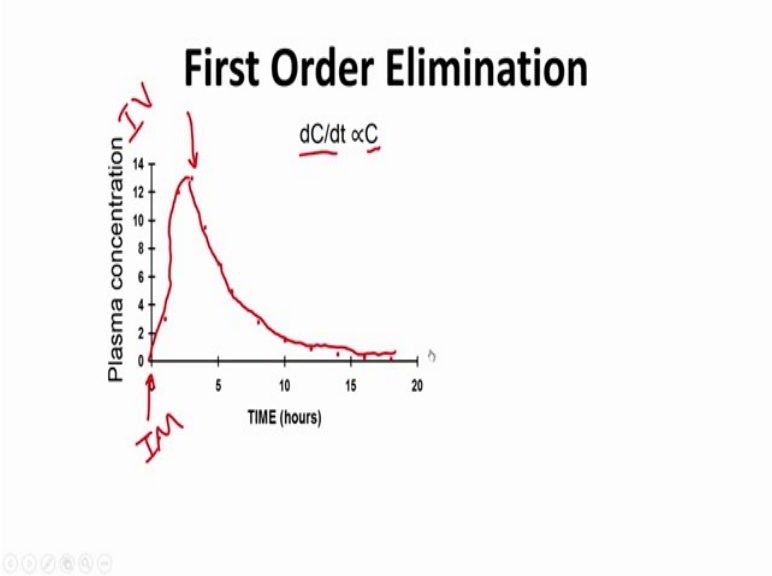

dC/dt ∝C

So, let us take a quick example here to get the kinetics. So, as we said that in first order elimination, we are saying that the rate of elimination is proportional to the concentration in the plasma. So, if I say the concentration in the plasma is C then rate of elimination is dC/dt and if I say that:

We get a profile like this which essentially when you inject the drug the plasma concentration goes up because let us say I inject the drug intramuscularly. So, the drug has to diffuse from the muscles, go into the blood vessel and build up the concentration there. So, this is kind of the absorption phase that you are seeing.

So, essentially at this time there was let us say an IM injection, intramuscular injection that was done and from this time to all the way up to here, the drug is building up in the IV intravenous and at the same time, it is also getting eliminated at some first order elimination because the concentration is increasing. But by this time we are saying that most of the drug that we injected into the muscularly has reached into the plasma. So, there is really no more drug coming from the depot that we had created intra muscularly and from that point we are saying that since the rate of elimination is proportional of the concentration. So, since the concentration is highest here, we have a rate that is very fast here, but as the drug concentration of the plasma is decreasing what we find is that the rate is also becoming slower and slower for the elimination.

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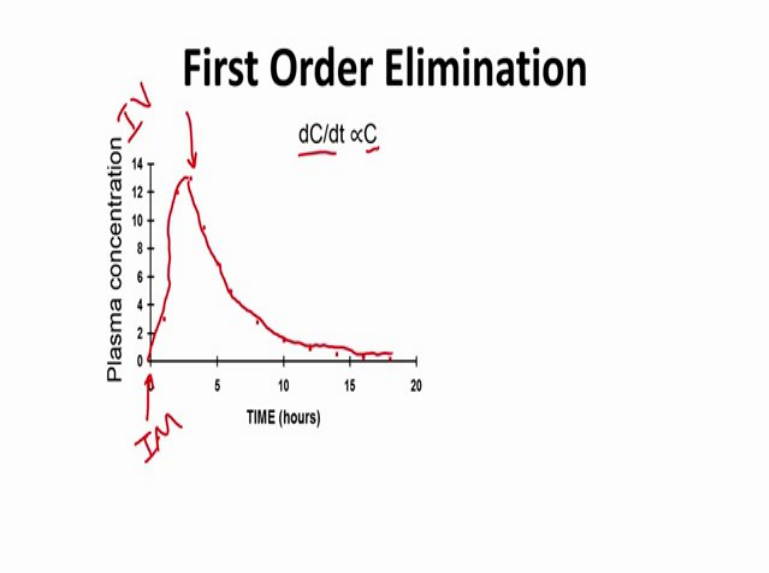

So, we get a curve something like this. So, we have to express it mathematically we are saying again that:

$$DC/dt = - k \cdot C$$

and if I have to integrate this what I can do is, I can separate out the variables. So, this will essentially becomes:

$dC = -kdt$

and then if I now integrate both sides the concentration of course, will be from time 0 to t and concentration let us say from the initial concentration of Co to some concentrations C at a time t.

If we do this we find that this gives an expression of Ct, this is a concentration of the time concentration at time t in the plasma:

$$C_t = C_0 \cdot e^{-K_{el} \cdot t}$$

So, if I take log on both side, I will essentially get:

$$\ln C_t = \ln C_0 - K_{el} \cdot t$$

So, if you look closely what is this term? This term is a variable. So, let us say this is y is equal to what is this term? This term is a constant because we had given a constant concentration initially. So, let us say A minus this we can consider as a slope. So, let us say m and this of course, is another variable t. So, this is let us say this is x. So, this essentially gives us a question of a straight line.

y=A-mx

So, what I am saying is if I plot this graph that I just plotted on to a log scale will essentially get a equation of a straight line and that is what essentially represented:

y=A-mx

So, that is what is written here.

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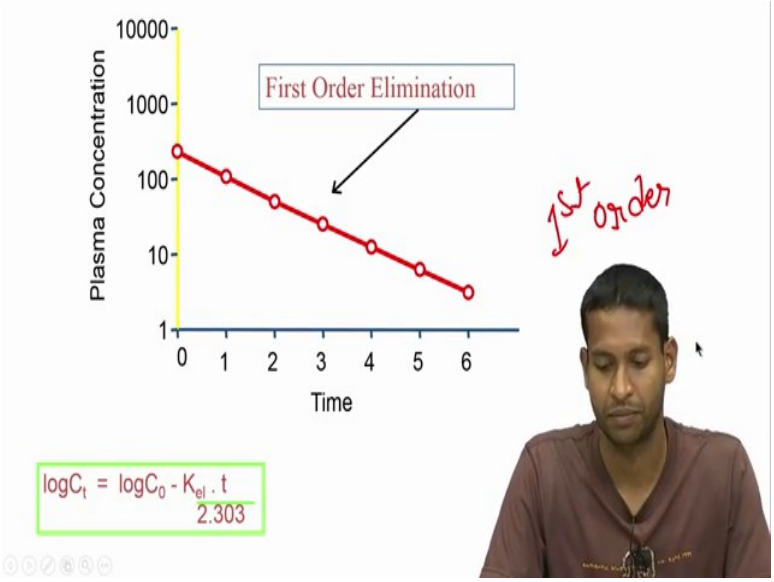

So, if I plot this on a log scale we essentially get and when I say log scale, it is a semi log scale because the plasma concentration is plotted on a log scale and time is plotted on a normal axis. So, we will essentially get a first order elimination which will be a straight line for this particular graph. So, if we able see a straight line for a drug elimination and then on a semi log scale; that means, it is a first order kinetics and this is the typical equation that is represented by it.

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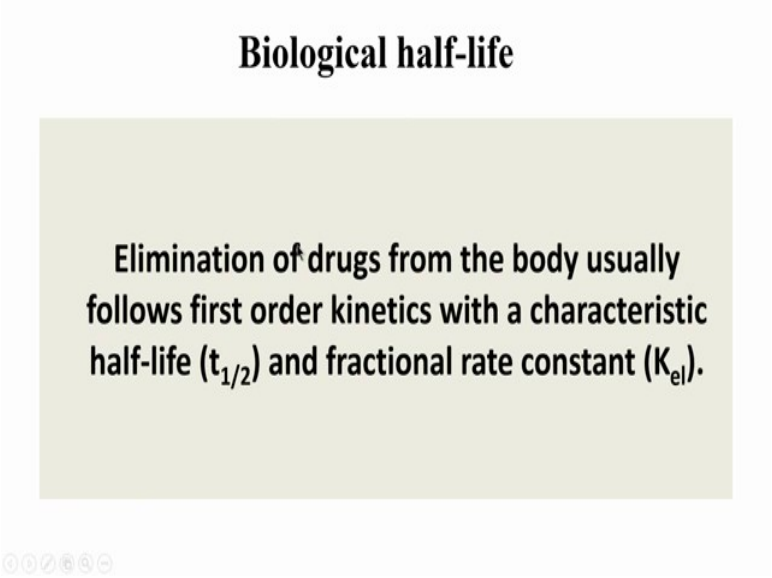

So, again we had talked about half-life before. So, if I have to express half-life in some other terms. This is essentially elimination of drugs from the body usually follows the first order kinetics with a characteristic half life and a fractional rate constant. So, let us say we have defined already this rate constant as K elimination.

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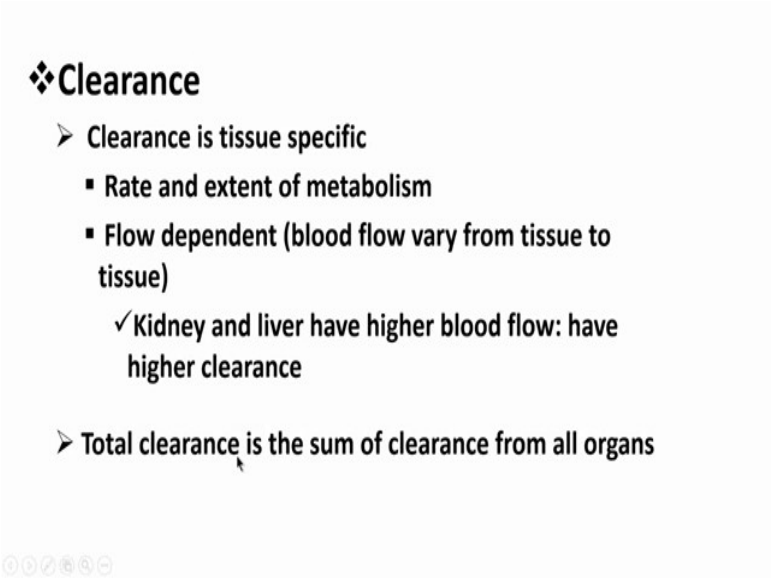

So, what is clearance? Clearance can be tissue specific. So, we can say clearance in the body that is in the whole body or we can say clearance through organ. So, let us say through blood or let us say through lungs, so, something like that. So, it will depend on what is the rate and

extent of the metabolism of the drug in that particular tissue. It will also be flow dependence. So, if a tissue is highly perfused; that means that the blood is going to constantly take it out. So, like kidney and liver a very high blood flow and have very high clearance and again the total clearance from the body is the sum of the total clearance from all the organs.

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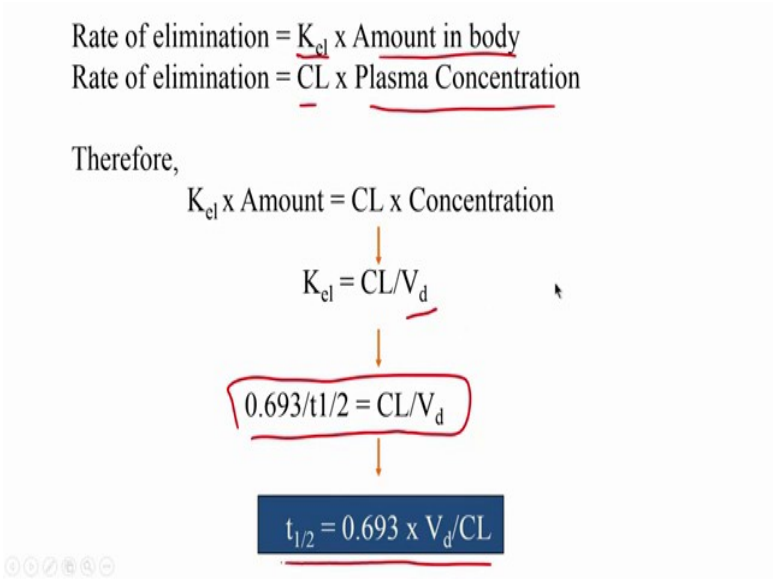

So,

Rate of elimination = K_{el} x Amount in body

The rate of elimination is also as we defined with clearance is:

Rate of elimination = CL x Plasma Concentration

So, therefore, if you equate these two, you essentially get an expression:

$$t_{1/2} = 0.693 \times V_d/CL$$

So, and remember what is Vd? Vd is the volume of the distribution that we discuss in the last class.

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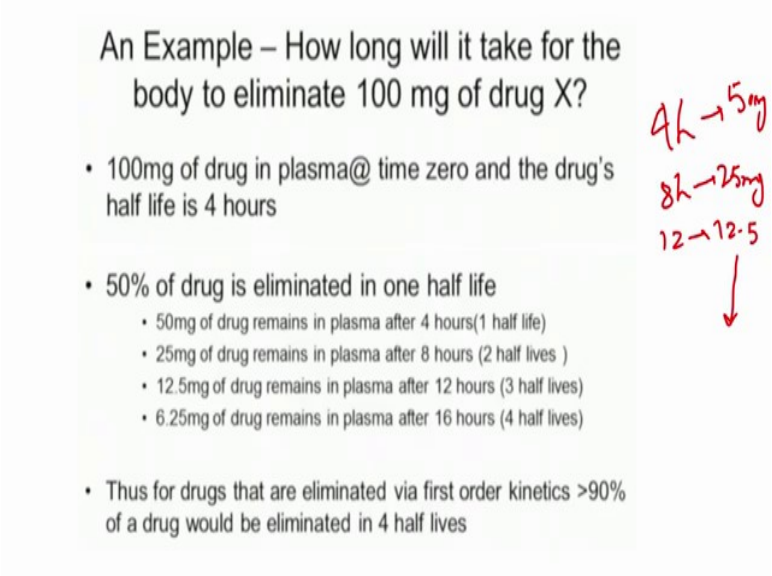

So, let us take another example. It is a very simple example. So, all we are interested at this point is to know how long will it take for the body to eliminate 100 milligram of drug X and the assumption here is that the 100 milligram of the drug is in the plasma at time 0 and a value that we are giving you is the drug half life is 4 hours.

So, I will give you guys another moment to kind of figure this out. It is a very simple thing. So, there are two ways to do this: one you can do it empirically. You can say that if the half life is 4 hours; so, we can say that in 4 hours the drug concentration will reduce to 50 milligram. In 8 hours this is going to reduce by half again. So, this is going to become 25 milligram and then we can further say that in 12 hours this is going to become 12.5.

So, if we continue to do this will eventually this value will continue to decrease, but remember this is not at this point because is always going to use by half you will never have the drug eliminate completely because this is always continue to reduce to infinitely small value, but it will never be 0, but that is not what happens typically. So, if we do this, we say that about as I described here continue to do this and will have in for half lives will have it down to 6.25.

So, if we say that how much it takes for it to remove above 90 percent of the drug? It will take about 4 half lives to get it down to below 90 percent and so, but then again when I said that it will never become 0 that is a theoretical case, but in actual cases it will become undetectable because you have a certain measurement that we are using, those concentration

might be therapeutically not even viable, may not be even have any significance practically to have concentrations reduced to that low amount. So, typically all drugs do get eliminated in due time.

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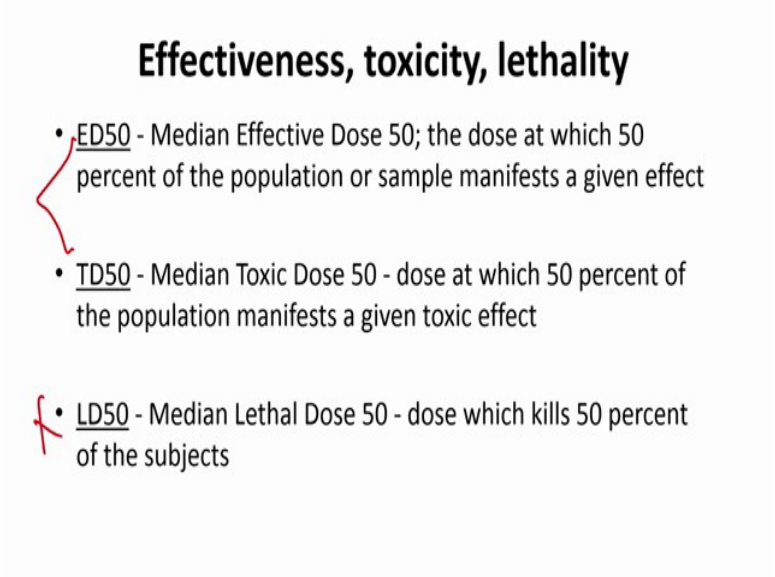

So, as I said we are going to define few more terms. These are terms again used quite a lot in medical fields as well as in the drug delivery areas. So, one is ED50 and what it means is the Effective Dose 50 and when we say that the drug has a ED50 of a certain value; that means, that at that particular dose almost 50 percent of the population will manifest a given effect.

So, again to give you an example, let us say if I have drug X and I say that it is used to reduce fever and somebody's having a fever then if I give the drug X to 100 people that are having fever, at the ED50 value of the drug, 50 people will have some sort of relief from the fever. So, that is called the Effective Dose 50, ED50. So, why is this important? Again, if I am a doctor trying to prescribe something I need to know what is the ED50 of the drug that I am prescribing. So, I need to prescribe higher dose than the ED50 because I want the patient to feel better.

Another term we are talking about is TD50 which is essentially Toxic Dose 50. This is also very important I do not want to give too much of a dose that it becomes toxic. So, again going back to the same example if I am giving a drug that has a dose that is equal to the TD50 of greater than TD50; that means, 50 percent of the people will manifest a toxic effect;

that could be vomiting, that could be depending on the drug that could have different toxic effects, but we do not want to really touch TD50.

So, now, if the doctors will prescribe something it will have to be between ED50 and TD50 because if it is more than TD50 then nearly half of the people will come back complaining about the toxicity and if it is less than ED50 then people won't even benefit. So, ideally we want the drugs to have a very wide gap between ED50 and TD50 because if the gap is lower then it is very hard for the doctors to prescribe the drug.

And finally, the last thing in terms of these terms that we are going to talk about is the LD50. And, then LD50 is essentially is the median Lethal Dose 50 which as the name suggests would mean that at this dose almost 50 percent of the subjects will actually die. So, that is something the doctors do not even want to come close to this. So, definitely is a no-no for the drug to reach this amount of concentration, but we do need to know what is the value so that the prescribers have some sort of estimate as to what is the concentration they never want to reach ok.

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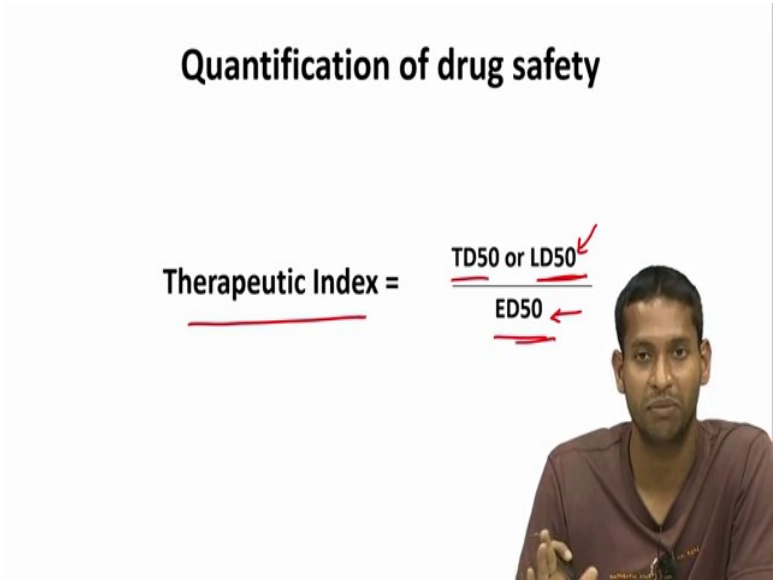

And, so, the way we quantify the drug is through this method which is essentially call a therapeutic index. So, a therapeutic index is nothing, but a dose at which:

Therapeutic Index = (TD50 or LD50)/ED50

So, essentially if I say the therapeutic index of the drug is high; that means, that it has quite a lot of high value of LD50 and low value of the ED50; that means, that the drug is good because at a very low concentration you are getting some therapeutic effect, but the LD50 is high. So, you can essentially work in the regime in between the two to prevent any toxicity to the patient.

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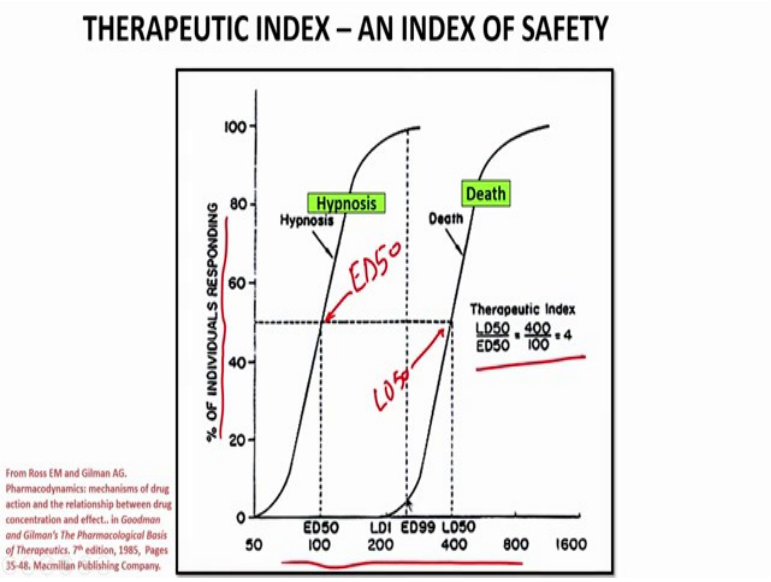

So, just an example here. So, these are typical curve that you will see. So, you have on the y-axis you have percent of in individuals are responding to the drug and on the x-axis you have concentration of the drug that was administered. So, what do you see typically is let us say this is a drug that is used to induce hypnosis in patient. And, so, as the concentration the drug is increasing you will see that more and more patients are becoming hypnotic which is, what is the outcome that is desired for this particular drug.

But, then at a certain high concentration; in this case this is just some random values; it is represented that as the concentration of the drug is increasing further, it may eventually cause even death in people. So, in this case the Lethal Dose 50 is right here because 50 percent the patient is dying at a concentration of above 400. So, the therapeutic index of the drug is essentially 400 by 100 because this value is the ED50 and then this value is the LD50.

So, the therapeutic index comes out to be 4 which is actually quite low for the drugs. They are typically used because let us see if you want 100 percent of the patients to respond we may have few people dying which is never desirable.

So, we will stop here. In the next class we will talk about some more things about TD50, LD50 and even talk about pro-drugs and all. So, we will see you next time.

Thank you.