Medicinal Chemistry
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Lecture No 40
Drug Administration Routes Part - 2

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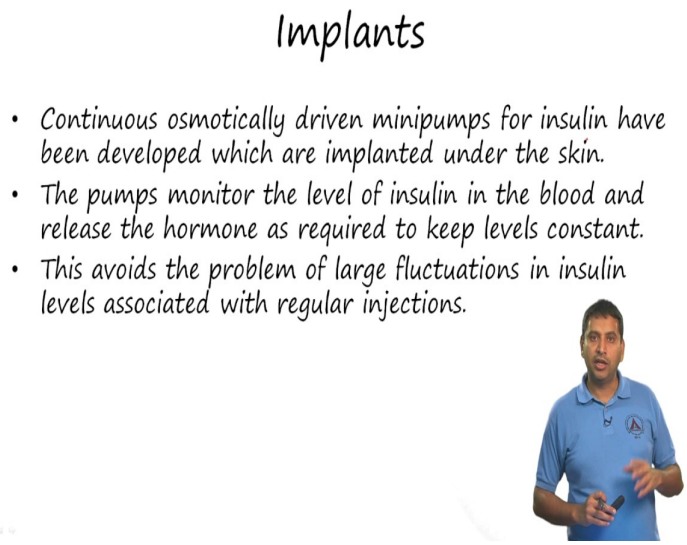

Another way to slow down release of a drug is to use implants. So there are many pumps which allow us to continuously administer the drug. So for example continuous osmotically driven mini pumps for insulin have been developed which are implanted under the skin.

So what these pumps do is that they monitor the level of insulin in the blood and release the hormone as required to keep the levels constant, right.

So one of the major problems with diabetes is the high level of fluctuation in blood sugar and insulin. And so these large fluctuations that are going to happen can be avoided.

And when insulin is administered through regular injections, the levels goes up substantially very soon and this is also a huge problem.

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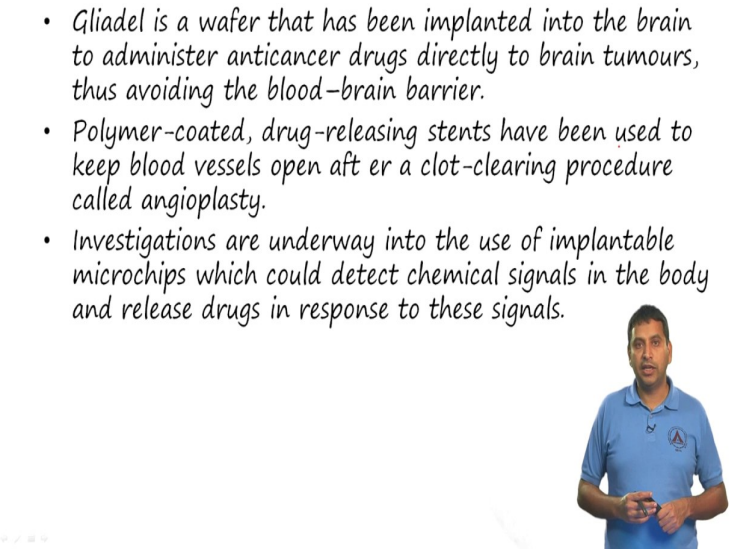

Gliadel is a wafer that has been implanted into the brain to administer anti-cancer drugs directly to brain tumours. And these can be used to avoid the blood brain barrier, Ok. There are also polymer-coated or drug releasing stents that have been used to keep blood vessels open.

So for example when there is a procedure of angioplasty the clot, the blood vessel has been cleared and then after that what is sometimes done is to put a stent which has a drug coated on it. So this will slowly release anti-coagulant for example.

Investigations are presently underway to use of implantable microchips which can detect chemical signals in the body and release drugs in response to these signals. So these are on-demand drug release type of situations.

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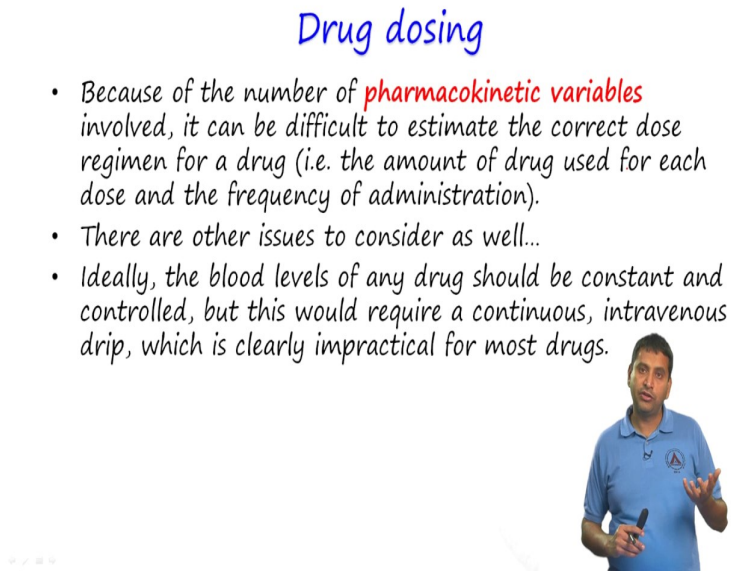

Now let us discuss the topic of drug dosing. So this is the amount of drug that needs to be given to a patient. Of course we have looked at number of pharmacokinetic variables and because of this large number it is sometimes difficult to estimate the correct dose regimen for a drug. Now how much of a drug to give, how often does one give it, all these are major issues.

So ideally the blood levels of any drug should be constant and controlled. But this would require a continuous intravenous drip which is clearly impractical for most drugs.

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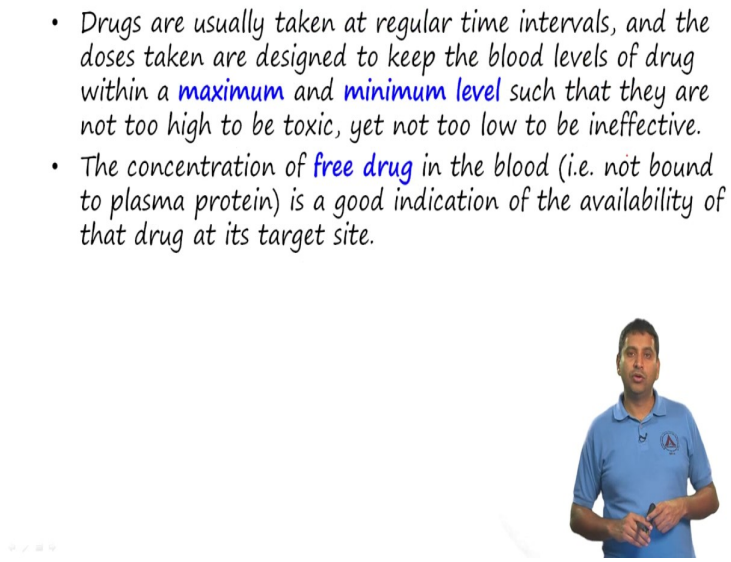

So drugs which we are commonly encountered or we are commonly used to are usually taken at regular intervals orally and these are designed to keep the blood levels of the drug within a maximum and a minimum level.

So it cannot go too high then what happens is that it can become toxic and it cannot be too low either, which will have it, make it ineffective.

So one of the parameters that we can measure is the concentration of free drug in the blood,

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- Drugs are usually taken at regular time intervals, and the doses taken are designed to keep the blood levels of drug within a **maximum** and **minimum level** such that they are not too high to be toxic, yet not too low to be ineffective.
- The concentration of **free drug** in the blood (i.e. not bound to plasma protein) is a good indication of the availability of that drug at its target site.

right, that is not bound to the plasma protein. So this gives us a good indication of the availability of the drug at its target site.

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- This does not mean that blood concentration levels are the same as the concentration levels at the target site.
- However, any variations in blood concentration will result in similar fluctuations at the target site.
- Blood concentration levels can be used to determine therapeutic and safe dosing levels for a drug.

Of course this does not mean that the blood concentration level is the same as the concentration level at its target site

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- This does not mean that blood concentration levels are the same as the concentration levels at the target site.
- However, any variations in blood concentration will result in similar fluctuations at the target site.
- Blood concentration levels can be used to determine therapeutic and safe dosing levels for a drug.

because we know that the target site invariably not always in the blood and they can be variation.

But any variations in the blood concentration will perhaps result in similar fluctuations in the target site. So therefore blood concentration levels are used reliably to determine what are known as therapeutic dose and safe dose for a drug.

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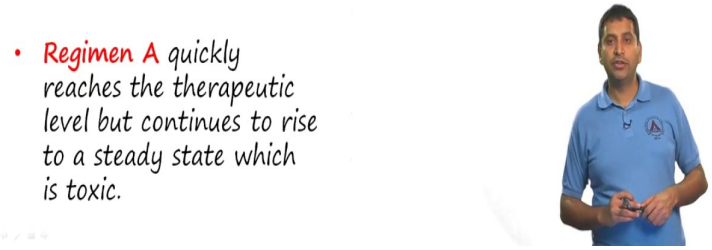

Now let us look at an example where we are providing a drug at a particular dose. So, so here is the plasma drug concentration. And here is the dose times; this gives you the number

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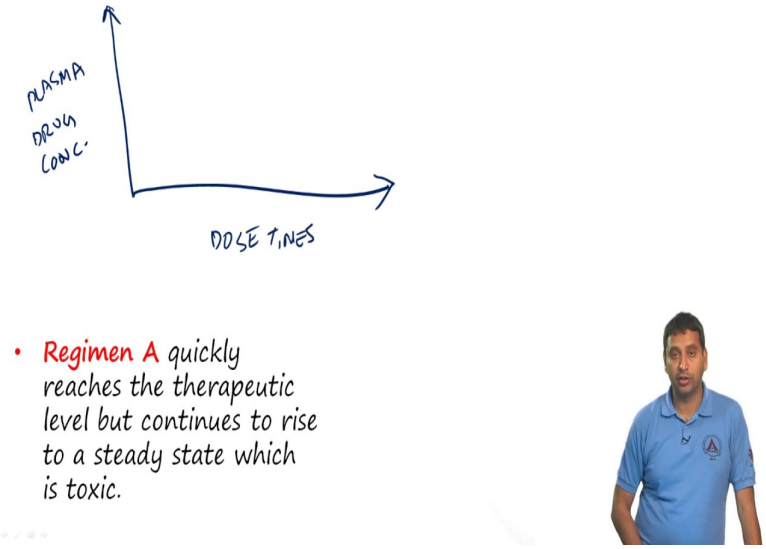

of doses.

So the first dose is given and so you could expect the drug concentration to go up, right and then due to metabolism and excretion it comes down.

So here is the second dose that is

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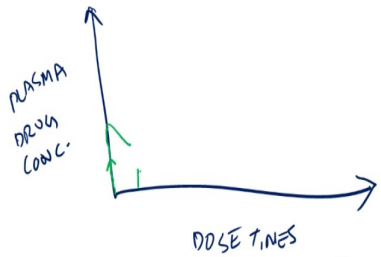

- Regimen A quickly reaches the therapeutic level but continues to rise to a steady state which is toxic.

given. It again goes up and then it starts to come down and then here is the third dose that is given,

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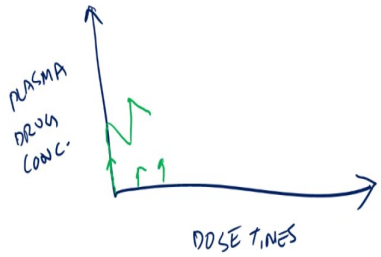

- Regimen A quickly reaches the therapeutic level but continues to rise to a steady state which is toxic.

and again goes up. And then it starts to come down. And then here is the fourth

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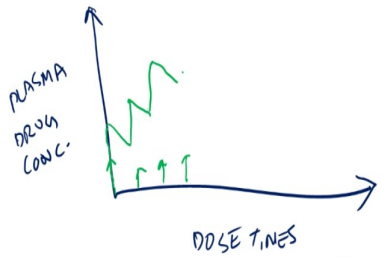

- Regimen A quickly reaches the therapeutic level but continues to rise to a steady state which is toxic.

dose given. Again it goes up and so on and so forth, right.

So what happens

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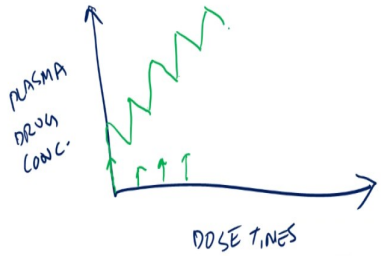

- Regimen A quickly reaches the therapeutic level but continues to rise to a steady state which is toxic.

is that as the dose increases

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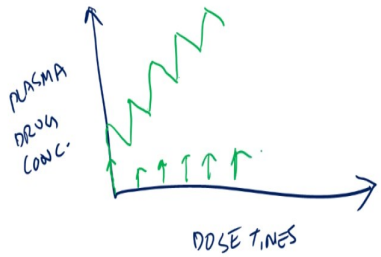

- Regimen A quickly reaches the therapeutic level but continues to rise to a steady state which is toxic.

you would have this type of a behavior, right. So at this plasma drug concentration level we can determine two important parameters.

Let us say this is the dose at which the compound is effective. That is, this is the therapeutic level. So

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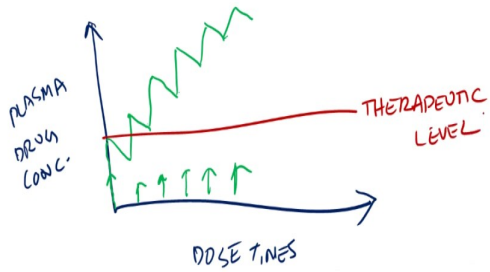

- Regimen A quickly reaches the therapeutic level but continues to rise to a steady state which is toxic.

you would want plasma drug concentration to be higher than the therapeutic level.

But let us say this is the toxic level. That means at this concentration or

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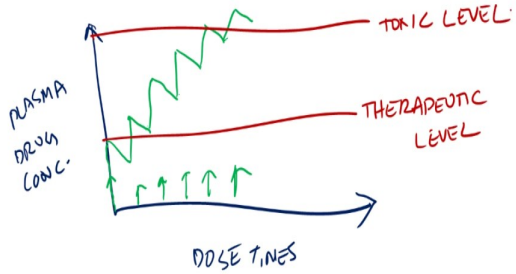

- Regimen A quickly reaches the therapeutic level but continues to rise to a steady state which is toxic.

above this concentration the drug is toxic. So therefore we would want to

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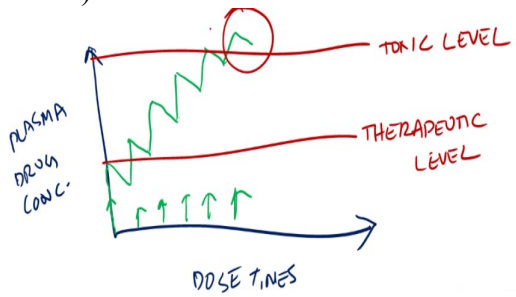

- Regimen A quickly reaches the therapeutic level but continues to rise to a steady state which is toxic.

avoid this region completely and dose it such that you are able to avoid going to the toxic level.

So this window is called the therapeutic window.

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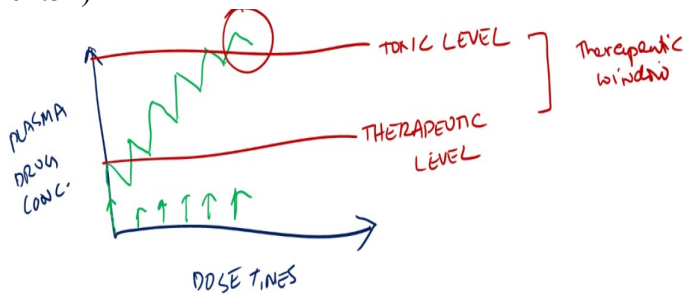

- Regimen A quickly reaches the therapeutic level but continues to rise to a steady state which is toxic.

So this regimen which we are going to call as regimen A,

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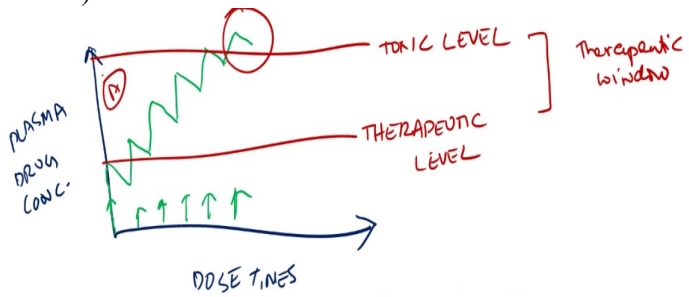

- Regimen A quickly reaches the therapeutic level but continues to rise to a steady state which is toxic.

here what happens is that it reaches the therapeutic level but continues to rise to a steady state where it is toxic.

Let us consider giving this drug at a lower dose. So here what we would do is to give essentially half the amount so when you start out at a lower range, goes up and then comes down, goes up. Second dose is given, comes down. Third dose is given, comes down. Fourth dose is given, comes down. Fifth dose is given, comes down and so on, right

So here if you call this as regimen B,

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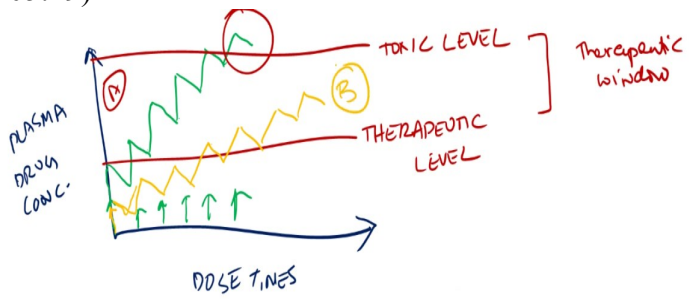

- Regimen A quickly reaches the therapeutic level but continues to rise to a steady state which is toxic.

in regimen B it takes longer for the compound or the drug to reach therapeutic level but it continues to be efficacious because it does not go into the toxic zone. So by changing the regimen one can figure out what is the right dosage to administer the drug at.

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- Dose regimen B involves half the amount of drug provided with the same frequency.
- The time taken to reach the therapeutic level is certainly longer, but the steady state levels of the drug remain between the therapeutic and toxic levels—the therapeutic window .

So dose B involves half the amount of drug provided with the same frequency. But the time taken to reach the therapeutic level is of course longer but the steady state levels of the drug remains between the therapeutic and the toxic levels.

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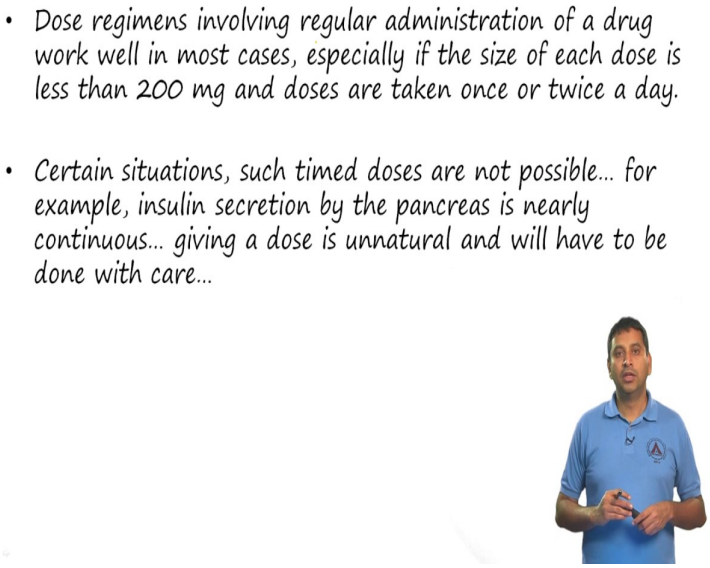

So dose regimens involving regular administration of a drug work well in most cases except especially if the dose is less than 200 milligram. And dose is taken once or twice daily.

But certain situations, such time doses are not possible. For example insulin secretion by pancreas is nearly continuous and so giving a dose is unnatural and will have to be done with care.

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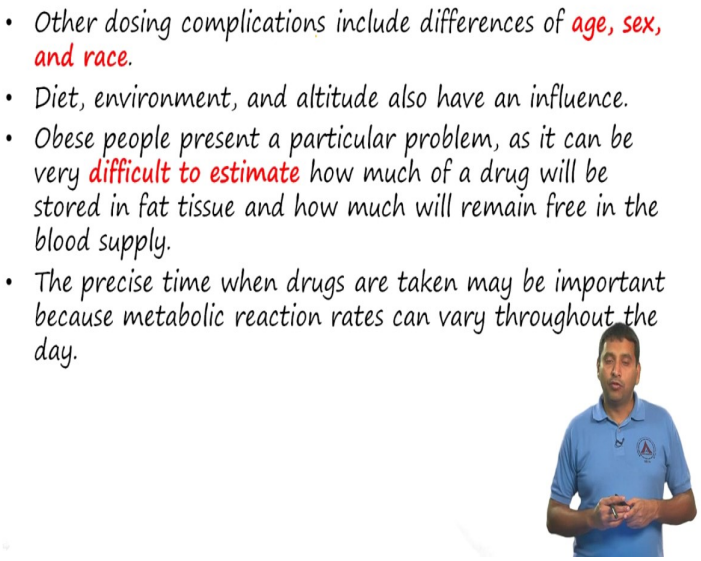

Of course there are other problems which are associated with age.

So the older the patient is, the more complicated the metabolism might be. There are gender issues and we have looked at previously there are also race issues.

And the diet, the food that is taken along with the medicine will have a profound impact. Of course the environment and altitude can also have important influence on the way in which the drug is going to act.

There is a class of population which are obese and these present a very peculiar problem because it is very difficult to estimate how much of the drug will be stored in the fat tissue, Ok.

And because there is some of it stored in the fat tissue and it is difficult to also estimate how much is ready, is free in the blood supply. So the precise time and drugs are taken, may be important because the metabolic reaction rates can vary throughout the day.

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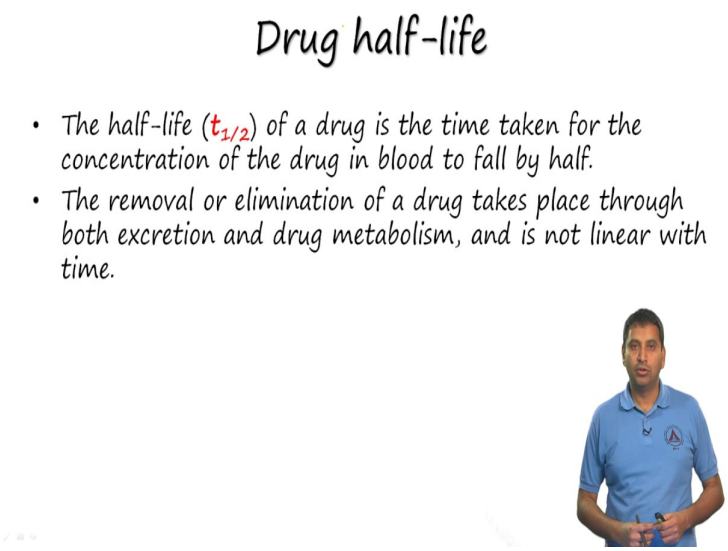

So the next important thing about the journey of a drug is the half life of a drug.

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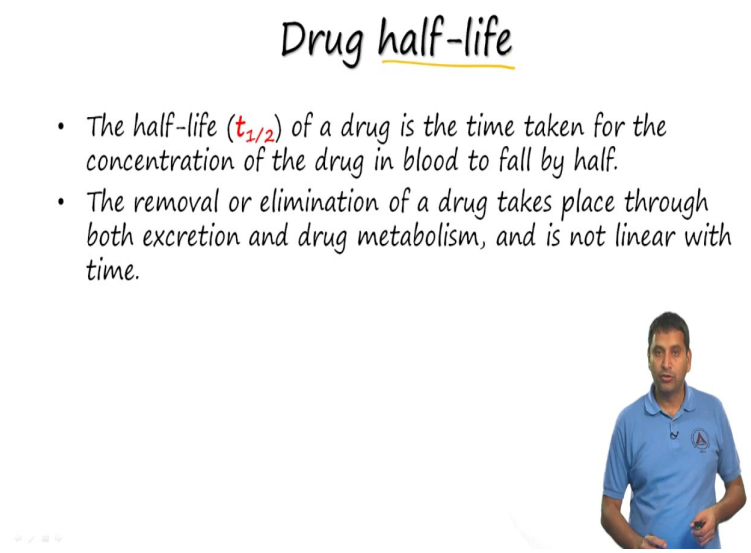

So half life is the time taken for the concentration of the drug to fall by half, Ok.

So you take a dose of let us say, 200 mg which contains some amount of active ingredient. How much of that active, how much time it takes for that active ingredient to reach 50 percent of the original concentration, right?

So this fall or removal or elimination can take place through excretion or metabolism, right. And as you can imagine it would not be linear, right.

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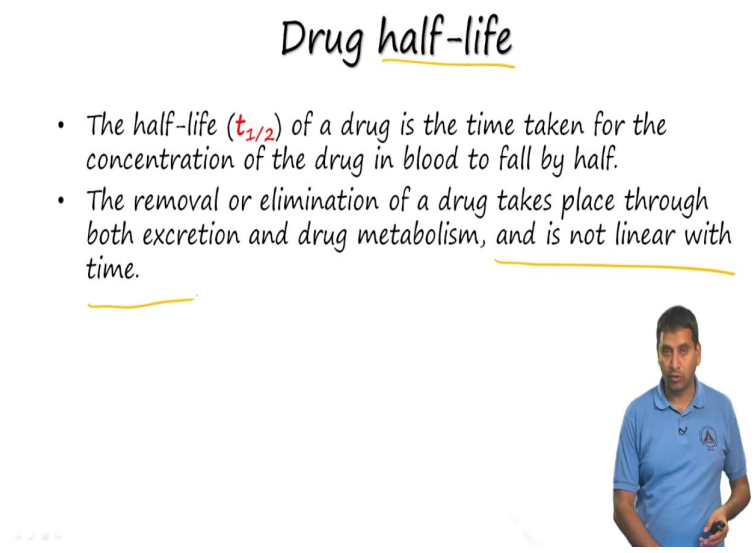

So you are not going to have a straight line that it is going to go down with time. And the metabolism is going to vary from person to person.

Some people may be excreting it out better; some people will have higher level of metabolism. But the drug half life is defined in the manner in which we look at the original concentration that the drug was given at and what is the time taken for it to fall by half.

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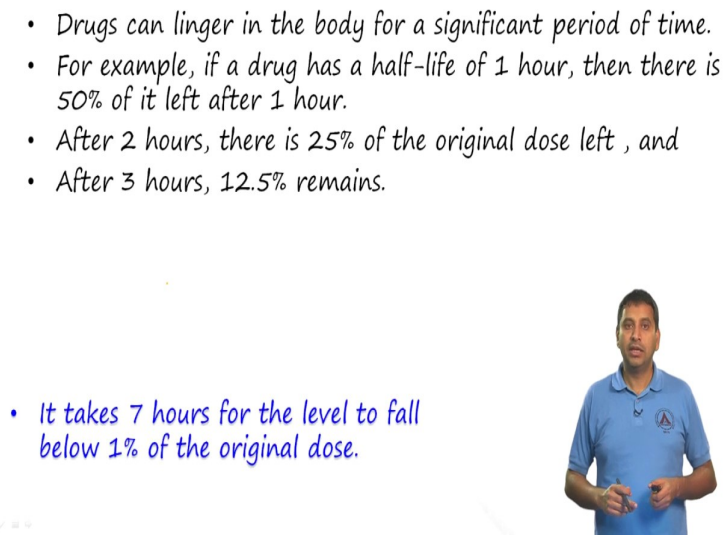

There are some drugs that can linger in the body for a long period of time, Ok but for example if a drug has a half life of about 1 hour,

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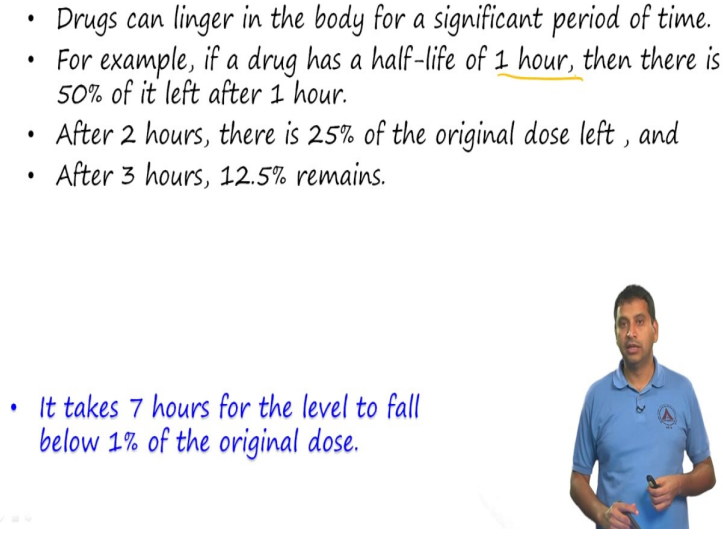

right then there is 50 percent of it left after 1 hour. So in the period of 2 hours there is 25 percent of the original dose

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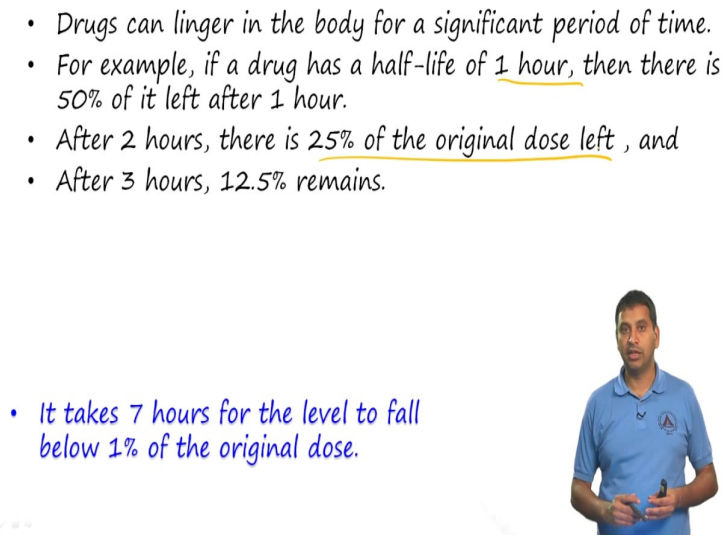

left. And in the period of 3 hours, 12 point 5 percent

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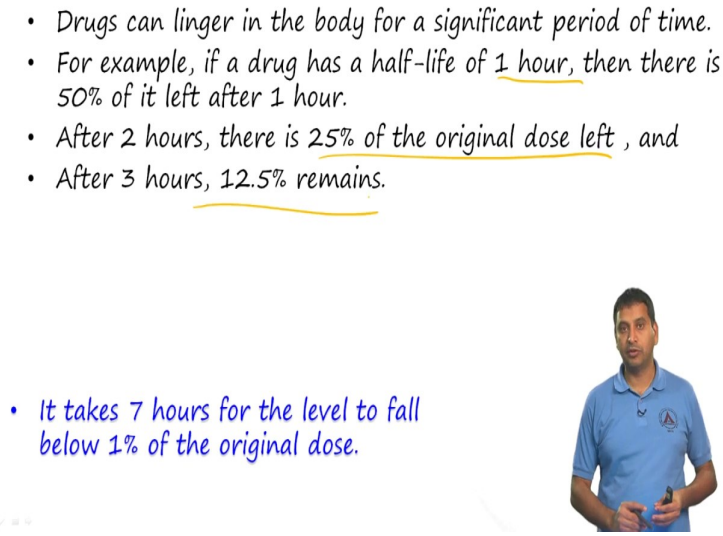

remains and so on, right.

So it takes a full 7 hours for the drug to fall below 1 percent of the original dose, Ok. So therefore once a drug is administered it can linger in the body for a pretty long time.

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- Some drugs such as the opioid analgesic fentanyl , have short half-lives (45 minutes), whereas others such as diazepam (Valium) have a half-life measured in days.
- When the half-life is in days, recovery from the drug may take a week or more

There are some drugs which are analgesic, for example the opiod analgesic fentanyl. They have very short half life of about 45 minutes, Ok and where as there are drugs like valium which have a half life measured in days, Ok.

So when the half life is in days, recovery from the drug may take a week or more. So having one dose of a drug can have take you many days to recover from that particular dose.

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Steady State Concentration

- Drugs are metabolized and eliminated as soon as they are administered, so it is necessary to provide regular doses in order to maintain therapeutic levels in the body.
- Therefore, it is important to know the half-life of the drug in order to calculate the frequency of dosing required to reach and maintain these levels.

Now let us define what is known as the steady state concentration.

So of course drugs are metabolized, eliminated as soon as they are administered. So it is necessary to provide regular doses of this drug. So we have already looked at this therapeutic level.

So in order to maintain this you need to be able to maintain a steady state concentration. Therefore it is important to know the half life of a drug in order to calculate the frequency of dosing, right. And for us to be able to ascertain how to reach that level, of therapeutic level and maintain these levels.

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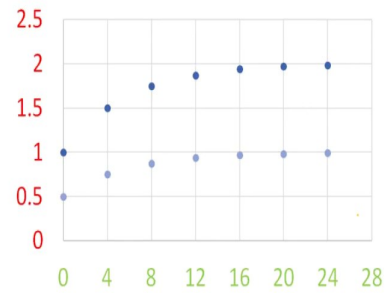

Time, hours	Max level	Min level
0	1	0.5
4	1.5	0.75
8	1.75	0.87
12	1.87	0.94
16	1.94	0.97
20	1.97	0.98
24	1.98	0.99

Note that there is a fluctuation in level in the period between each dose. The level is at a maximum aft er each dose and falls to a minimum before the next dose is provided.

So here is an example of a drug. What has been done here is that you take various time points and you administer a drug and it is a number of administrations that have occurred. And so what you do is you measure what is known as maximum level after let us say 3 or 4 attempts.

And then you measure what is known as a minimum level. So this is the maximum

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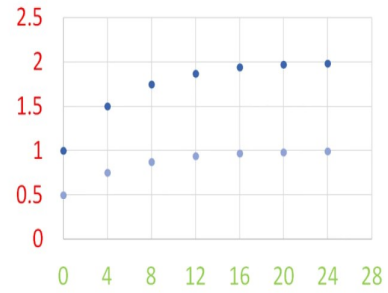

Time, hours	Max level	Min level
0	1	0.5
4	1.5	0.75
8	1.75	0.87
12	1.87	0.94
16	1.94	0.97
20	1.97	0.98
24	1.98	0.99

Note that there is a fluctuation in level in the period between each dose. The level is at a maximum aft er each dose and falls to a minimum before the next dose is provided.

level and this is the minimum level.

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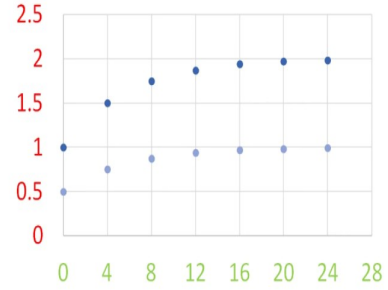

Time, hours	Max level	Min level
0	1	0.5
4	1.5	0.75
8	1.75	0.87
12	1.87	0.94
16	1.94	0.97
20	1.97	0.98
24	1.98	0.99

Note that there is a fluctuation in level in the period between each dose. The level is at a maximum aft er each dose and falls to a minimum before the next dose is provided.

And at a interval of 4 hours, you measure the amount of drug, right. So in certain cases you will find that the maximum level and the minimum level

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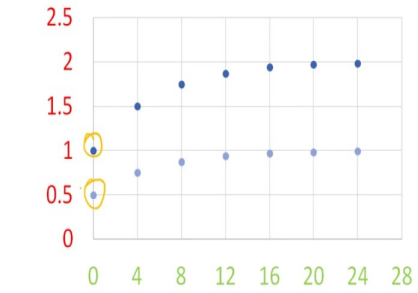

Time, hours	Max level	Min level
0	1	0.5
4	1.5	0.75
8	1.75	0.87
12	1.87	0.94
16	1.94	0.97
20	1.97	0.98
24	1.98	0.99

Note that there is a fluctuation in level in the period between each dose. The level is at a maximum aft er each dose and falls to a minimum before the next dose is provided.

there is a fluctuation, right.

So once you administer the drug, the maximum level let us say goes to this, y axis is micro gram per mL and this is time in hours,

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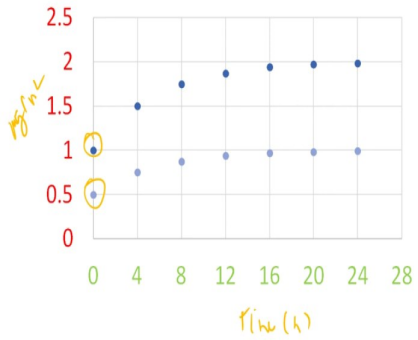

Time, hours	Max level	Min level
0	1	0.5
4	1.5	0.75
8	1.75	0.87
12	1.87	0.94
16	1.94	0.97
20	1.97	0.98
24	1.98	0.99

Note that there is a fluctuation in level in the period between each dose. The level is at a maximum aft er each dose and falls to a minimum before the next dose is provided.

Ok.

So in, the drug goes up to the highest dose it can go up to, is 1 micro gram per level. And the lowest level is 1, is point 5 micro gram per level. So if you plot the maximum level, it goes over here like this,

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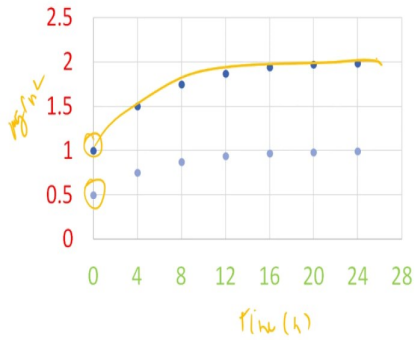

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8	1.75	0.87
12	1.87	0.94
16	1.94	0.97
20	1.97	0.98
24	1.98	0.99

Note that there is a fluctuation in level in the period between each dose. The level is at a maximum aft er each dose and falls to a minimum before the next dose is provided.

Ok.

And similarly if you plot the minimum level it goes like this,

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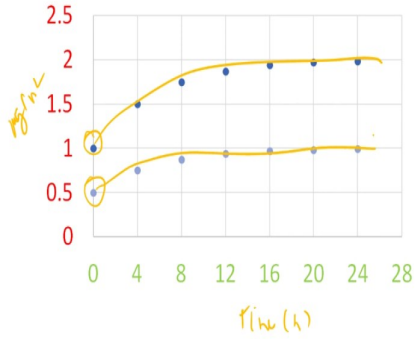

Time, hours	Max level	Min level
0	1	0.5
4	1.5	0.75
8	1.75	0.87
12	1.87	0.94
16	1.94	0.97
20	1.97	0.98
24	1.98	0.99

Note that there is a fluctuation in level in the period between each dose. The level is at a maximum aft er each dose and falls to a minimum before the next dose is provided.

right. There is the fluctuation in the level, in the period between each dose, Ok. The level is at a maximum after each dose and then falls to the minimum before the next dose is provided.

Of course it is important to ensure that the level does not drop below the therapeutic level but does not rise beyond a particular point so that side effects are induced.

So in this case it would be ideal if the therapeutic window is somewhere here.

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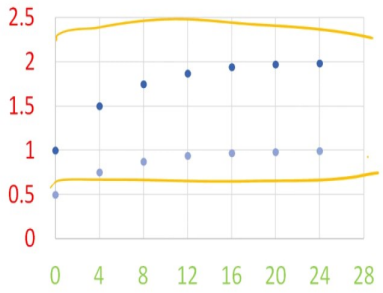

It is important to ensure that the level does not drop below the therapeutic level but does not rise to such a level that side effects are induced.

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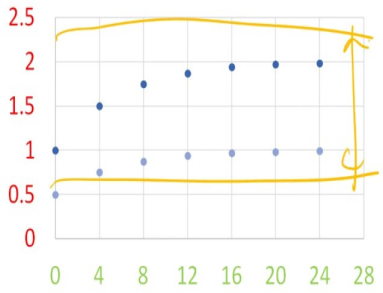

It is important to ensure that the level does not drop below the therapeutic level but does not rise to such a level that side effects are induced.

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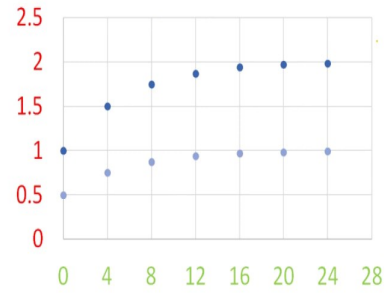

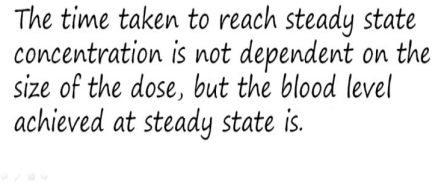

The time taken to reach steady state concentration is not dependent on the size of the dose but the blood level achieved as the steady state is.

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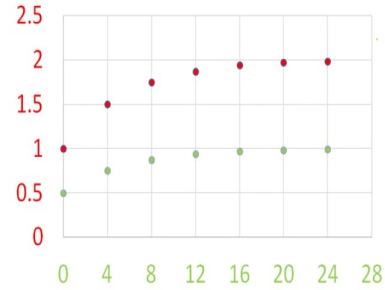

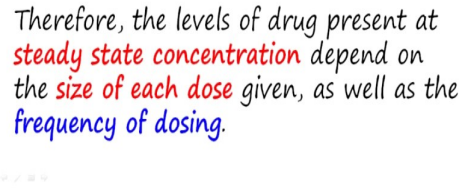

Therefore the levels of the drug present at steady state concentration depend on the size of each dose given as well as the frequency of dosing.

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- During clinical trials, blood samples are taken from patients at regular time intervals to determine the concentration of the drug in the blood.
- This helps determine the proper dosing regime in order to get the ideal blood levels.

Before a drug is actually released into the market there are clinical trials that are conducted. So here blood samples are taken from patients at regular time intervals to determine the concentration of the drug

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- During clinical trials, blood samples are taken from patients at regular time intervals to determine the concentration of the drug in the blood.
- This helps determine the proper dosing regime in order to get the ideal blood levels.

in the blood. This helps us determine the proper dosing regime in order to get the ideal blood levels.

So you do not want the level to go up beyond the, the, you know the toxic zone. At the same time we did not want it to be too low there is no therapeutic efficiency.

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- The **area under the plasma drug concentration curve** (**AUC**) represents the total amount of drug that is available in the blood supply during the dosing regime.

So there is something called as the area under the plasma drug concentration, which is called as the AUC which represents the total amount of drug that is available in the blood supply during the dosing regimen. We look at this concept later in the course.

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Drug tolerance

- With certain drugs, it is found that the effect of the drug
- diminishes after repeated doses...
- The size of the dose needs to be increased in order to achieve the same results.
- This is known as drug tolerance.

There is a concept wherein people have, do not respond to the same dose of the drug which is called as drug tolerance. And with certain drugs this is observed and it is found that the effect of the drug diminishes after repeated doses.

So what needs to be done is that you need to increase the size of the dose to see the same result, Ok. So this effect is called

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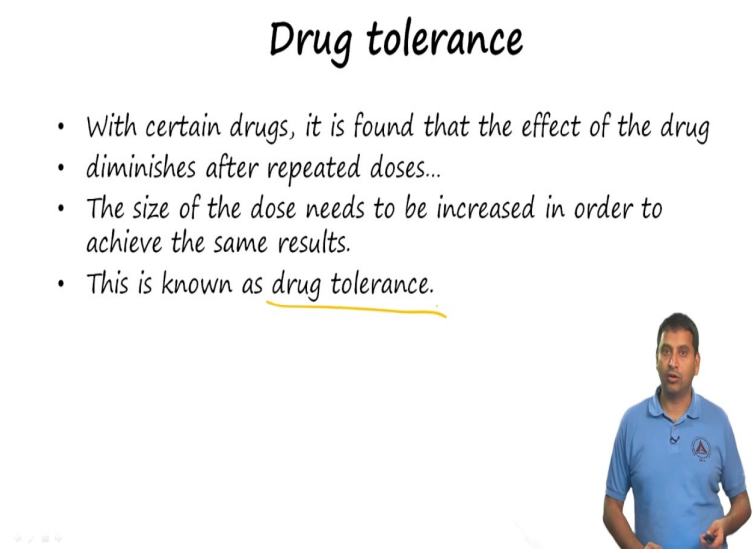

as drug tolerance.

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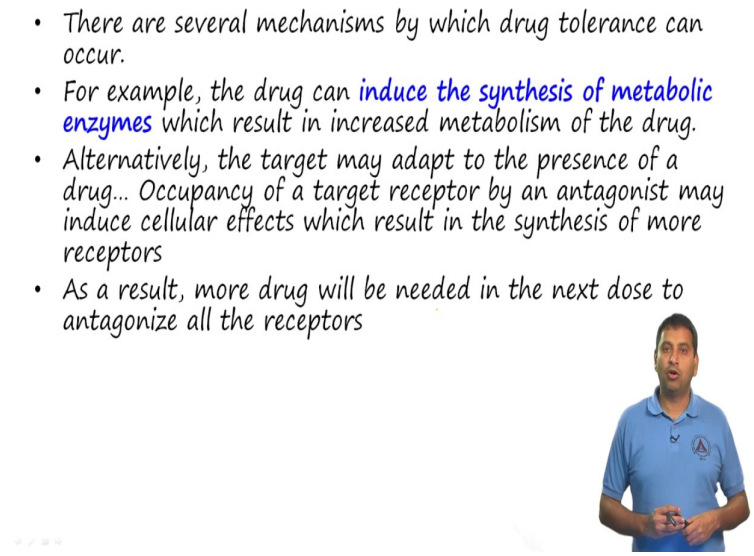

It is commonly observed in certain types of drugs, for example when in pain killers and so on. And there are several mechanisms by which drug tolerance can occur.

So for example it can induce the synthesis of metabolic enzymes which result in increased metabolism of the drug. So once the metabolism of the drug increases then what you need to do, what you need is a higher dose of the drug for it to reach the therapeutic efficiency.

Another possibility is that the target may adapt to the presence of a drug. So for example occupancy of the target receptor by an antagonist may induce cellular effects which result in the synthesis of more receptors, Ok.

So let us say you have the receptor on the surface on which you want to have an antagonist. Now instead of having 2 receptors you may have 5 receptors that are produced, right.

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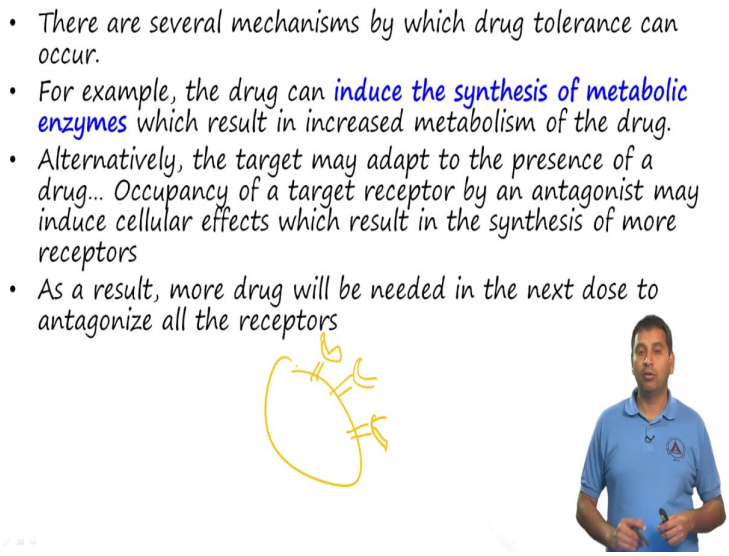

So this, what, that is you need a larger dose of the drug to achieve the same effect, to antagonize.

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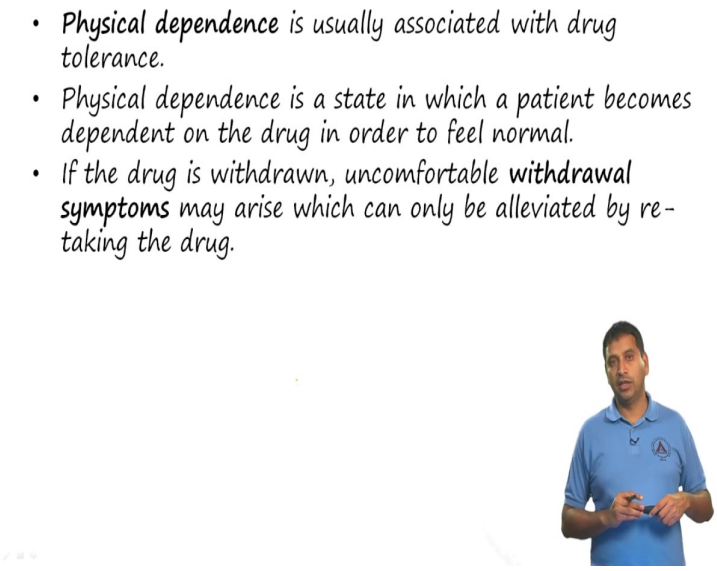

There is a concept called as physical dependence which is associated with drug tolerance.

So it is a state in which a patient becomes dependent on the drug in order to feel normal, Ok. So if you remove the drug then there are lots of uncomfortable withdrawal symptoms.

So you would have heard for example there are drug addicts who are extremely uneasy in the absence of the drug, right. And you would need to give the drug to the person for alleviating the symptoms.

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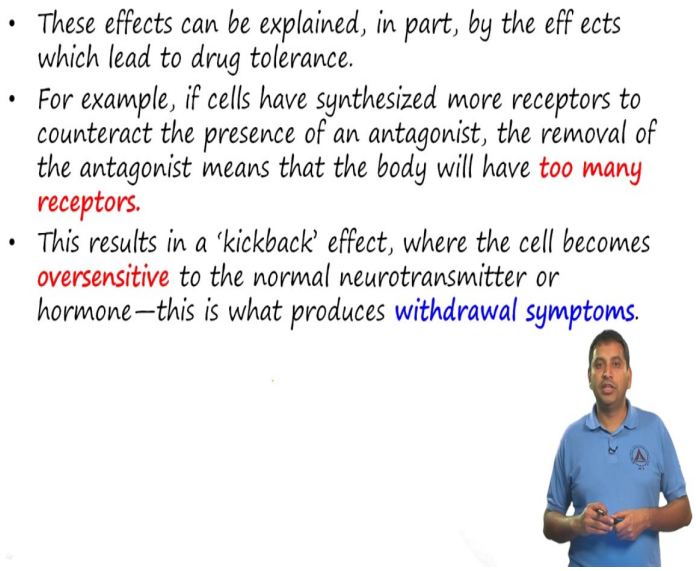

So these effects can in part be explained by drug tolerance.

So for example if the cells have synthesized more receptors to counteract the presence of an antagonist, now if remove the antagonist the cell has too many receptors, Ok. And so what happens is that this results in what is known as the kickback effect.

That means there is a stronger effect now because the cells have become over-sensitive to the normal neurotransmitter, Ok. And this is what produces the

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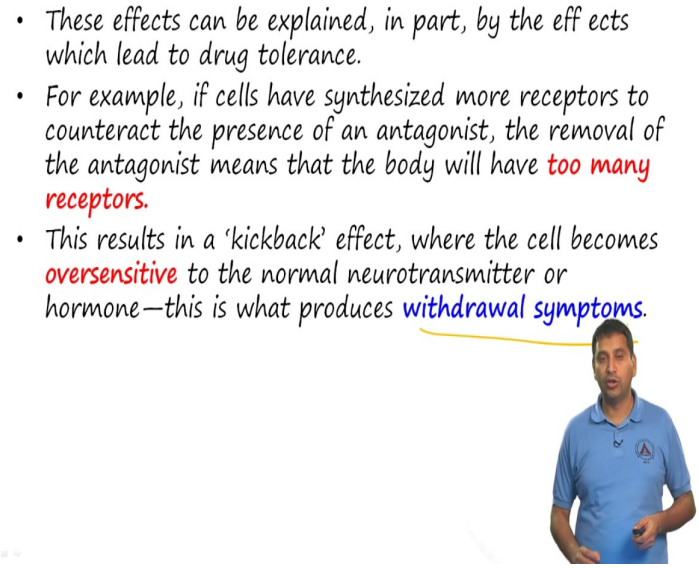

so-called withdrawal symptoms.

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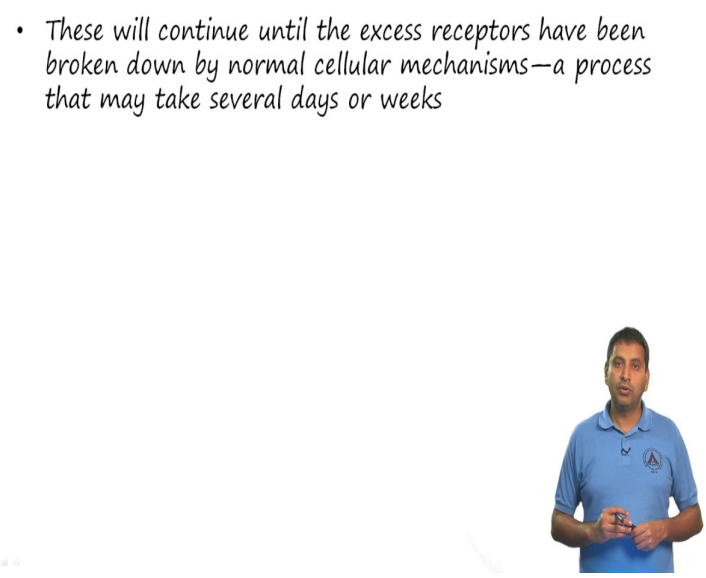

This will happen for some time until those excess receptors have been broken down by normal cellular mechanisms and then it restores normalcy. But this process may take several days or weeks. And so the withdrawal symptoms which are extremely uncomfortable and sometimes very difficult to overcome may take several days or even weeks.

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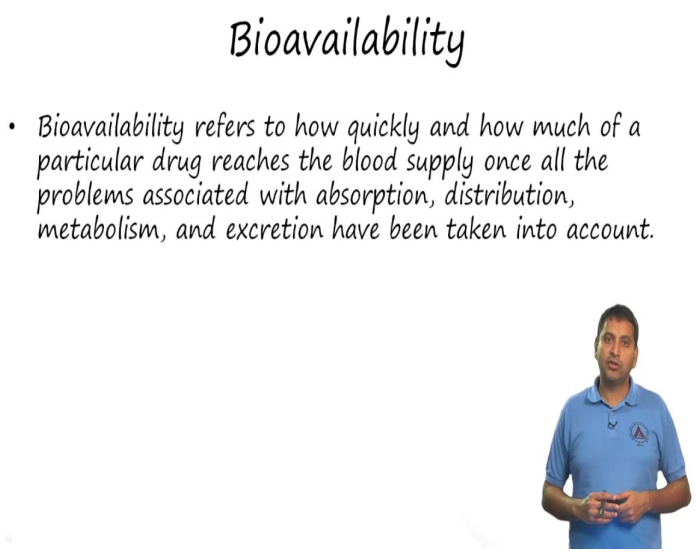

The next concept that we need to understand is bioavailability, Ok. So bioavailability refers to how quickly and how much of a particular drug reaches the blood supply, right.

So once you have taken care of all the problems associated with absorption, distribution, metabolism and excretion then bioavailability is the amount of drug that gets into it and how quickly into the blood.

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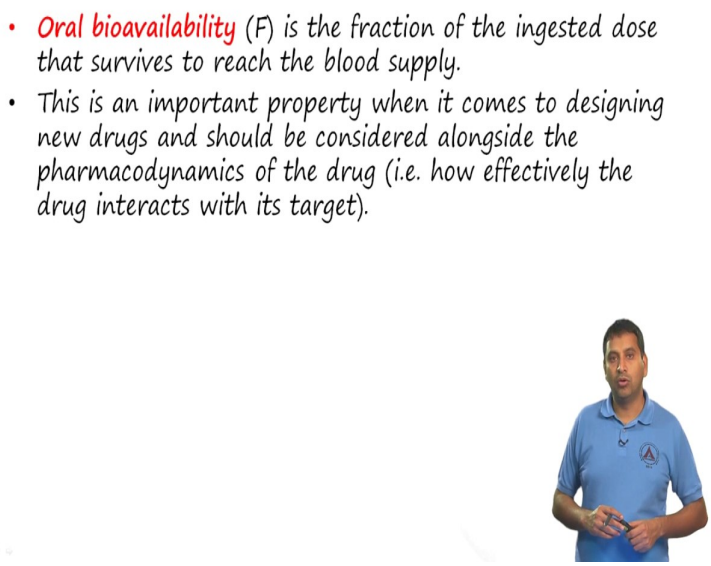

So oral bioavailability is the fraction of the ingested dose that survives to reach the blood supply, right.

So let us say you take

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- Oral bioavailability (F) is the fraction of the ingested dose that survives to reach the blood supply.
- This is an important property when it comes to designing new drugs and should be considered alongside the pharmacodynamics of the drug (i.e. how effectively the drug interacts with its target).

100 micro gram and only 5 micro gram reaches then the oral bioavailability is 5 divided by 100 and it is the fraction of the amount of drug that reaches the blood supply.

This is a very important property when it comes to designing new drugs and of course it should also be considered very strongly along with pharmacodynamics that is how effectively the drug interacts with its target.

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Formulation

- The way a drug is formulated can avoid some of the problems associated with oral administration.
- Drugs are normally taken orally as tablets or capsules.

Another important concept in this part of the course is formulation. So this is the way in which the drug is actually administered. So sometimes a drug is formulated in such a way that it can avoid some of the problems associated with oral administration, Ok.

So as you know drugs are normally taken as tablets or capsules.

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- A tablet is usually a compressed preparation that contains 5–10% of the drug, 80% of fillers, disintegrants, lubricants, glidants, and binders, and 10% of compounds which ensure easy disintegration, disaggregation, and dissolution of the tablet in the stomach or the intestine—a process which is defined as the pharmaceutical phase of drug action.

Tablet is a compressed preparation that contains about may be 5 to 10 percent of the drug and about 80 percent of other fillers.

And there are some disintegrants, lubricants, glidants and binders and so on and about 10 percent of compounds which ensure easy disintegration, disaggregation and dissolution of the tablet in the stomach or the intestine.

This is a process which is defined as the pharmaceutical phase of the drug action. Of course we will not be spending much time on this part of the course. There is an entire industry which revolves around how to be able to deliver the drug or administer the drug in a very efficient manner.

So there are pills that can also be coated with sugar, varnish or wax that helps us disguise the taste. Because some of the drugs are extremely bad-tasting and this helps us ensure that the drug is properly consumed.

Many of us have taken drugs in a capsule. A capsule is nothing but a gelatinous envelope which encloses the active substance, Ok. And this capsule can be designed to remain intact for some hours after ingestion in order to delay absorption, Ok.

You can also have a mixture of slow and fast release particles to produce rapid as well as sustained absorption in the same dose.

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- Such factors as particle size and crystal form can significantly affect dissolution.
- Fast dissolution is not always ideal.
- For example, slow dissolution rates can prolong the duration of action or avoid initially high plasma levels.

There are number of factors such as particle size, the form of crystal that can significantly affect how well the drug dissolves, Ok.

So sometimes fast dissolution is not ideal and you would like to have slow dissolution. And this will avoid high levels of the drug in the plasma. And it can also help us prolong the duration of action.