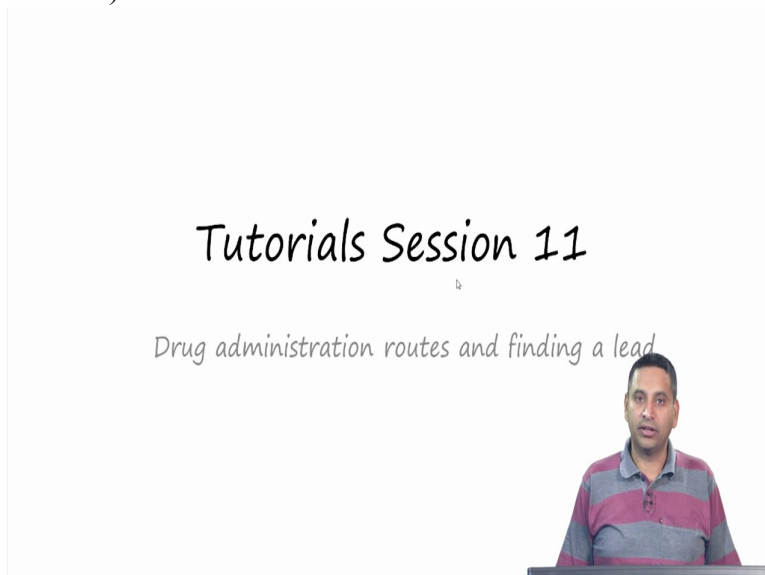


Medicinal Chemistry
Professor Dr. Harinath Chakrapani
Department of Chemistry
Indian Institute of Science Education and Research Pune
Lecture No 44
Tutorial -11 Drug Administration Routes and Finding a Lead

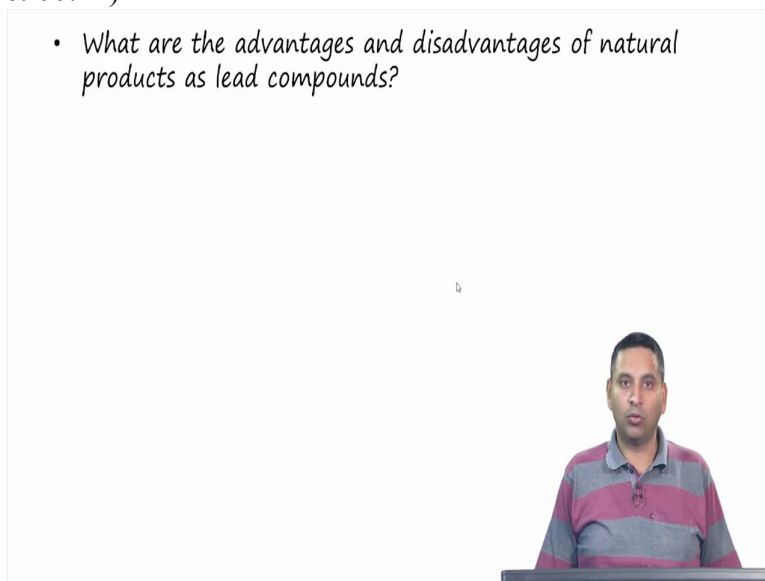
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So in today's tutorial session we will be solving some problems related to drug administration routes in finding a lead.

So the first question here is

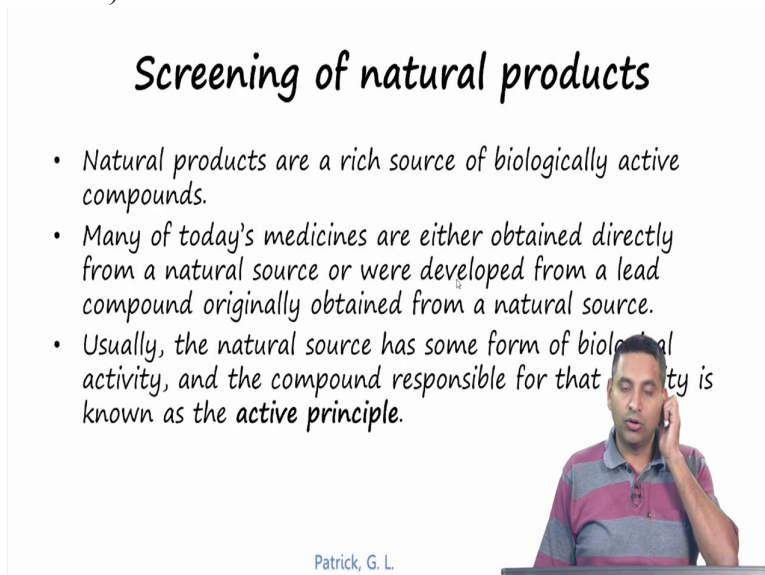
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what are the advantages and disadvantages of natural products as lead compounds?

So in order to address this question let us go back to the topic that we discussed in the previous lectures.

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Screening of natural products

- *Natural products are a rich source of biologically active compounds.*
- *Many of today's medicines are either obtained directly from a natural source or were developed from a lead compound originally obtained from a natural source.*
- *Usually, the natural source has some form of biological activity, and the compound responsible for that activity is known as the **active principle**.*

Patrick, G. L.

So screening of natural products is a very good way to identify biologically active compounds. And as we have come to realize a number of today's medicines are actually either obtained directly from natural source or were developed from a lead compound that is originally obtained from a natural source.

So the main component of the natural source that is active is called the active principle. So it is this active principle that we are really interested in because that is a single molecule that is going to have the desired biological properties.

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- Such a structure can act as a lead compound.
- Most biologically active natural products are **secondary metabolites** with quite **complex structures** and several **chiral centres**.
- This has an advantage in that they are extremely **novel compounds**.



So this structure which is the active principle can act as a lead compound.

So the number of these natural products are actually what are known as secondary metabolites. And they have quite complex structures. And we have looked at several examples where they have a number of chiral centers.

So we have already discussed that chiral centers are not very desirable to have in a drug because you will have to isolate and you have to synthesize the other isomer and test that as well.

So when you have a complex natural product which has a chiral centre then it makes it difficult to synthesize. So this has an advantage because these compounds are typically very novel.

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- The advantages of natural products as lead compounds are as follows:
 - There is a greater chance of finding physiologically active compounds in nature since there is often an evolutionary advantage in an organism producing a physiologically active compound (e.g. as a defence chemical).
 - Many natural compounds have totally novel structures which have not been synthesised before.
 - Many natural compounds (e.g. toxins) are quite complex in nature with a highly rigid structure where the compound is locked into the active conformation or limited to a relative few number of conformations. This can result in high potency and selectivity for the target.



So to summarize the advantage of natural products are there is a greater chance of finding physiological relevant compound in nature

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- The advantages of natural products as lead compounds are as follows:
 - There is a greater chance of finding physiologically active compounds in nature since ~~there is often an evolutionary advantage in an organism producing a physiologically active compound (e.g. as a defence chemical).~~
 - Many natural compounds have totally novel structures which have not been synthesised before.
 - Many natural compounds (e.g. toxins) are quite complex in nature with a highly rigid structure where the compound is locked into the active conformation or limited to a relative few number of conformations. This can result in high potency and selectivity for the target.



because this is an evolutionary advantage for the organism.

So imagine that there is a biological warfare going on between one set of organisms and another set of organisms, typically microbes. And one of those microbes is going to win.

That means that one of the microbes is going to do something to get rid of the other one. So these are typically physiologically active compounds that are isolated. And they are used in self-defense.

So the other advantage is that they have totally novel structures

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- The advantages of natural products as lead compounds are as follows:
 - There is a greater chance of finding physiologically active compounds in nature since there is often an evolutionary advantage in an organism producing a physiologically active compound (e.g. as a defence chemical).
 - Many natural compounds have totally novel structures which have not been synthesised before.
 - Many natural compounds (e.g. toxins) are quite complex in nature with a highly rigid structure where the compound is locked into the active conformation or limited to a relative few number of conformations. This can result in high potency and selectivity for the target.



which have not been synthesized before. So that makes it very attractive. And there are also toxins for example which are secreted by organisms sometimes and they are also quite complex in nature with a highly rigid structure.

And now when the compound is locked into the active conformation or they are limited to a relatively few number of conformations, so this

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- The advantages of natural products as lead compounds are as follows:
 - There is a greater chance of finding physiologically active compounds in nature since there is often an evolutionary advantage in an organism producing a physiologically active compound (e.g. as a defence chemical).
 - Many natural compounds have totally novel structures which have not been synthesised before.
 - Many natural compounds (e.g. toxins) are quite complex in nature with a highly rigid structure where the compound is locked into the active conformation or limited to a relative few number of conformations. This can result in high potency and selectivity for the target.



can result in very high potency and selectivity for the target.

So these are some of the advantages. So by using a natural product there is a high chance that you can have totally novel compounds and they have also evolved in self-defense and so it is possible that some of these compounds may be active.

And there are toxins which have been deliberately synthesized and they are quite complex in nature. And sometimes they are highly rigid. And they are designed; they are synthesized to be present in the active conformation to hit a particular target.

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- The disadvantages include the following:
 - The natural product may only be present in small quantities in the natural source, restricting its availability.
 - Isolating and purifying a natural product from its natural source tends to be **slow, tedious and costly**.
 - The complexity of many natural products makes their synthesis impractical on a commercial basis. This in turn makes it difficult to produce analogues of the natural product.



So these are some of the advantages. Now the disadvantage is that the natural product is typically isolated in very small quantities. So they are present in very small quantities. And typically from kilograms of the natural source if you are lucky you will isolate a few milligram.

So this is also a very slow and tedious process and it can prove to be quite expensive depending on the source of the compound. Also because they are so complex, natural product synthesis make is very challenging, especially if you have 6, 7, 8, 9 chiral centers you need to make a natural product as a single enantiomer which is very challenging.

So therefore making this on a commercial basis is nearly impractical. Also because it is impractical to make it, making analogs of the natural product is also difficult. So these are some of the advantages and disadvantages of using natural products.

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- Explain how aquaporins work to transport water



Next question is; explain how aquaporins work to transport water.

So we have discussed this

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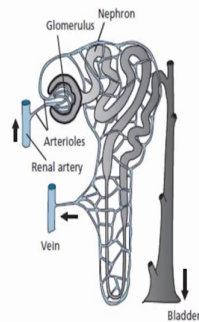
- Explain how aquaporins work to transport water



in class. Aquaporins are a class of proteins which help with transporting water. Now in order to understand or to address this question let us go back and look at how kidneys function.

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- Blood enters the kidneys by means of the **renal artery**.
- This divides into a large number of capillaries, each one of which forms a knotted structure called a **glomerulus** that fits into the opening of a duct called a **nephron**

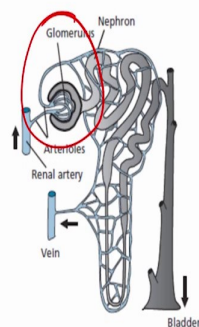


So when the blood enters the kidneys by the means of the renal artery, then what happens is that they divide into larger number of capillaries and this in turn goes and forms a knotted structure called the glomerulus.

So the glomerulus

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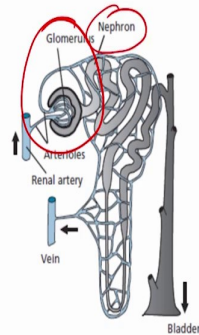
- Blood enters the kidneys by means of the **renal artery**.
- This divides into a large number of capillaries, each one of which forms a knotted structure called a **glomerulus** that fits into the opening of a duct called a **nephron**



is shown here, Ok and this glomerulus then sits in the duct which is called a nephron. So this is the nephron

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- Blood enters the kidneys by means of the **renal artery**.
- This divides into a large number of capillaries, each one of which forms a knotted structure called a **glomerulus** that fits into the opening of a duct called a **nephron**



as shown here. So therefore the blood that enters the kidneys is going to form this kind of a structure.

Now

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- The blood entering these glomeruli is under pressure, and so plasma is forced through the pores in the capillary walls into the nephron, carrying with it any drugs and metabolites that might be present. Any compounds that are too big to pass through the pores, such as plasma proteins and red blood cells, remain in the capillaries with the remaining plasma.



since it is entering under pressure then what happens is that because there are small pores on the capillary wall, the plasma is forced through these pores. So along with the plasma, any drug that is present in the plasma is also carried along with it, or other metabolites.

And so any compound that is too big to pass through these pores such as plasma proteins and red blood cells remain in the capillaries while all others are expelled.

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- Note that this is a filtration process, so it does not matter whether the drug is polar or hydrophobic: all drugs and drug metabolites will be passed equally efficiently into the nephron.
- However, this does not mean that every compound will be excreted equally efficiently, because there is more to the process than **simple filtration**.



So this is a filtration process.

So here it really does not matter whether the drug is polar or hydrophobic. And all drugs and drug metabolites will be passed equally efficiently into the nephron.

However this does not mean that every compound will be excreted with equal efficiency because there is more than a simple filtration process that is involved.

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- The filtered plasma and chemicals now pass through the nephron on their route to the bladder.
- However, only a small proportion of what starts that journey actually finishes it.



So the filtered plasma and chemicals now pass through the nephron on to their route to the bladder. However only a small portion of what starts the journey finishes it.

This is because

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- This is because the nephron is surrounded by a rich network of blood vessels carrying the filtered blood away from the glomerulus, permitting much of the contents of the nephron to be reabsorbed into the blood supply.
- Most of the water that was filtered into the nephron is quickly reabsorbed through pores in the nephron cell membrane which are specific for water molecules and bar the passage of ions or other molecules.
- These pores are made up of protein molecules called *aquaporins*.



the nephron is surrounded by a rich network of blood vessels carrying the filtered blood away from the glomerulus. So therefore the contents of the nephron can be reabsorbed into the blood supply.

So, most of the water that was filtered into the nephron is quickly reabsorbed through the pores on the cell membrane which are very specific for water molecules.

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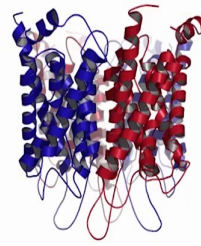
- This is because the nephron is surrounded by a rich network of blood vessels carrying the filtered blood away from the glomerulus, permitting much of the contents of the nephron to be reabsorbed into the blood supply.
- Most of the water that was filtered into the nephron is quickly reabsorbed through pores in the nephron cell membrane which are specific for water molecules and bar the passage of ions or other molecules.
- These pores are made up of protein molecules called *aquaporins*.



And these do not allow passage of ions or other molecules. And these are the pores that we are interested in and these are called as aquaporins.

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- Aquaporins, also called **water channels**, are integral membrane proteins from a larger family of major intrinsic proteins that form pores in the membrane of biological cells, mainly facilitating transport of water between cells.
- The cell membranes of a variety of different bacteria, fungi, animal and plant cells contain aquaporins through which water can flow more rapidly into and out of the cell than by diffusing through the phospholipid bilayer.
- Six membrane spanning alpha helical domain with both carboxylic and amino terminal on cytoplasmic side.
- Two hydrophobic loops contain conserved asparagine proline alanine motif



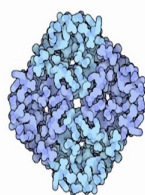
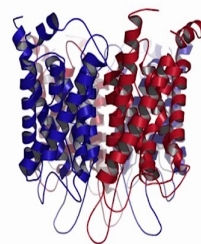
Aquaporins also known as water channels are integral membrane components and they form a larger family of major intrinsic proteins that form pores in the membrane of biological cells.

So the main function of these aquaporins is to facilitate transport of water between cells. Cell membranes of a variety of different bacteria, fungi, animal and plant cells contain aquaporins through which water can flow.

So 6 membrane spanning alpha-helical domain which both contain carboxylic and amino terminal on the cytoplasmic side is present. And then there are two hydrophobic loops which contain conserved asparagine, proline, alanine motif.

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- Six membrane spanning alpha helical domain with both carboxylic and amino terminal on cytoplasmic side.
- Two hydrophobic loops contain conserved asparagine proline alanine motif
- Aquaporins selectively conduct water molecules in and out of the cell, while preventing the passage of ions and other solutes.
- Aquaporins are integral membrane pore proteins



So these aquaporins help in selectively conducting water in and out of the cell while preventing the passage of ions or other solutes. Therefore aquaporins are important components in this process.

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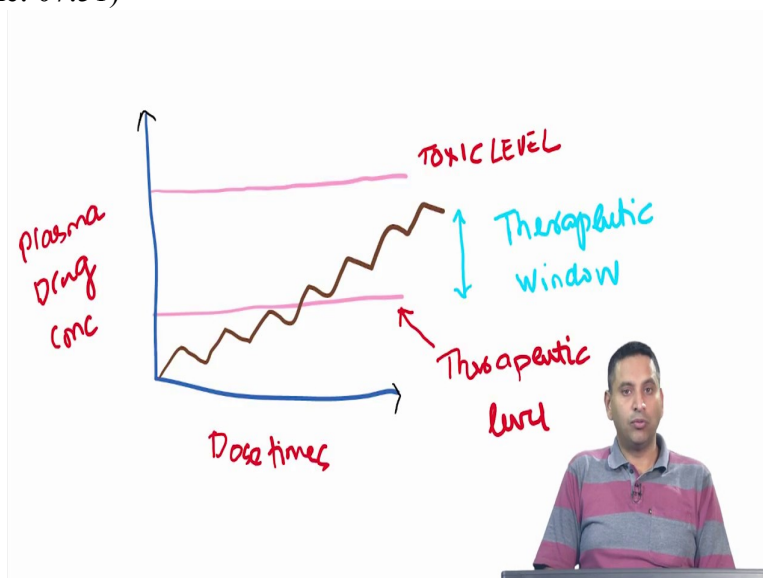
- Explain the concept of therapeutic window



The next question is, explain the concept of therapeutic window.

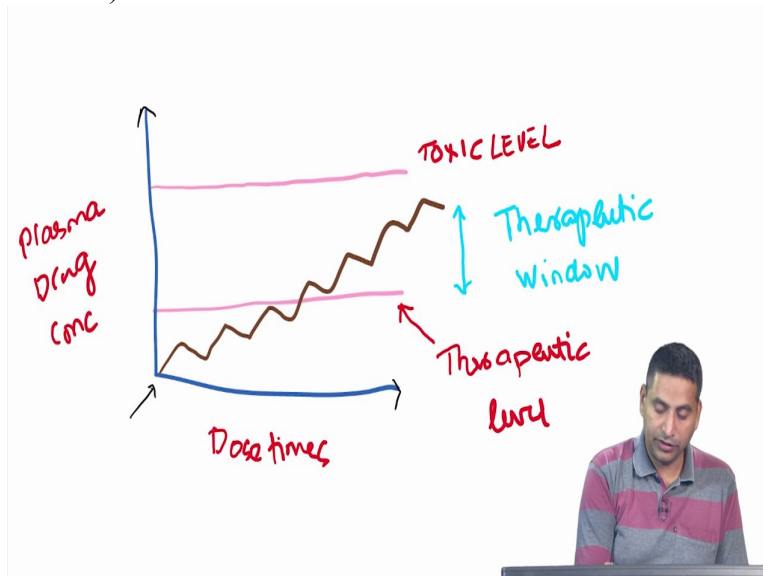
So in order to address this question let us draw a plot.

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So when a drug is administered on the x-axis here

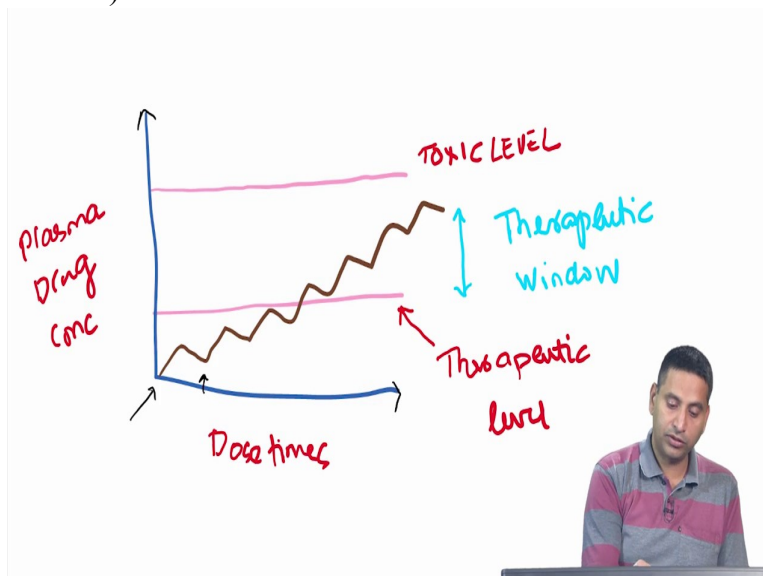
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is the number of doses.

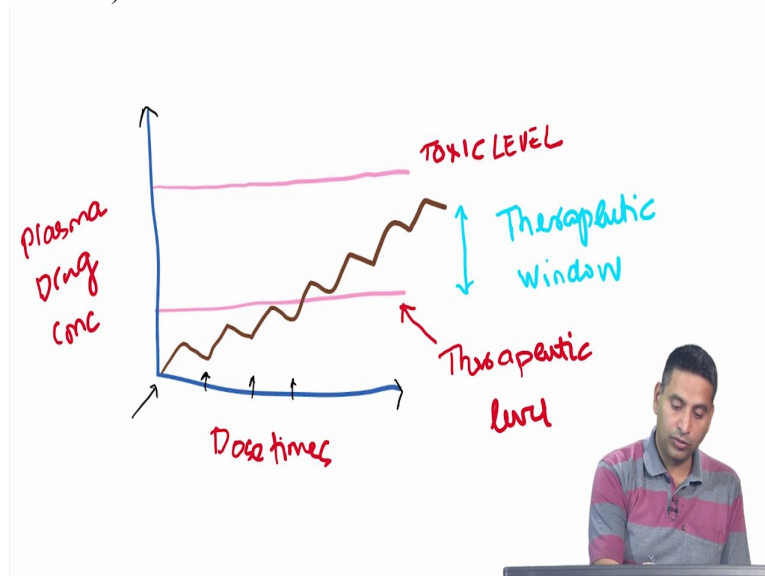
So here basically you give a dose

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and then there is another

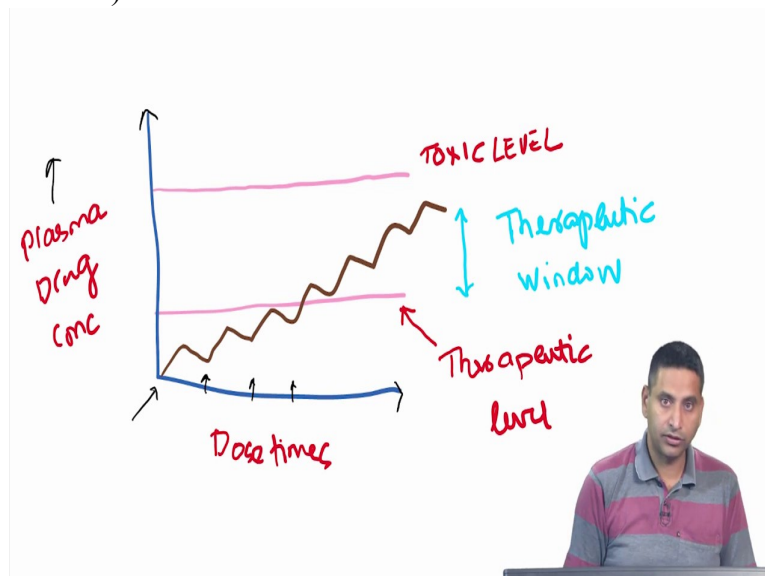
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dose that is given here, another dose that is given here and so on, Ok.

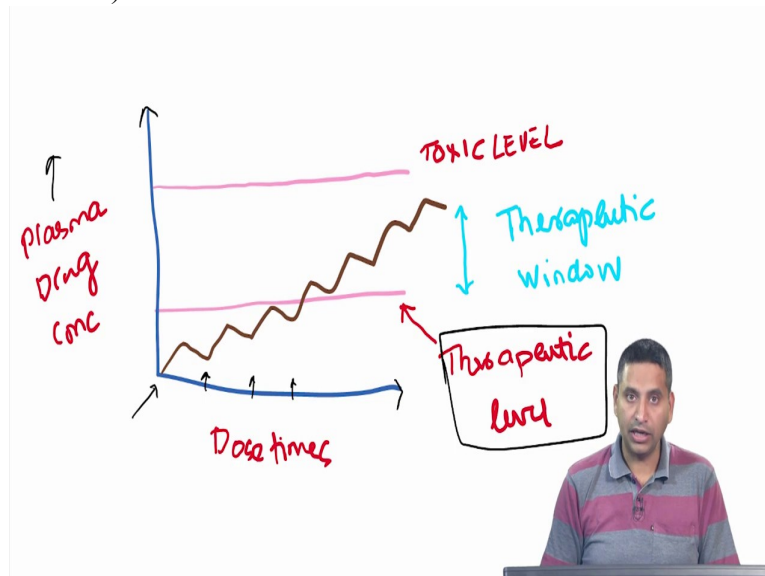
And then what we do is we measure the plasma drug concentration on the y axis.

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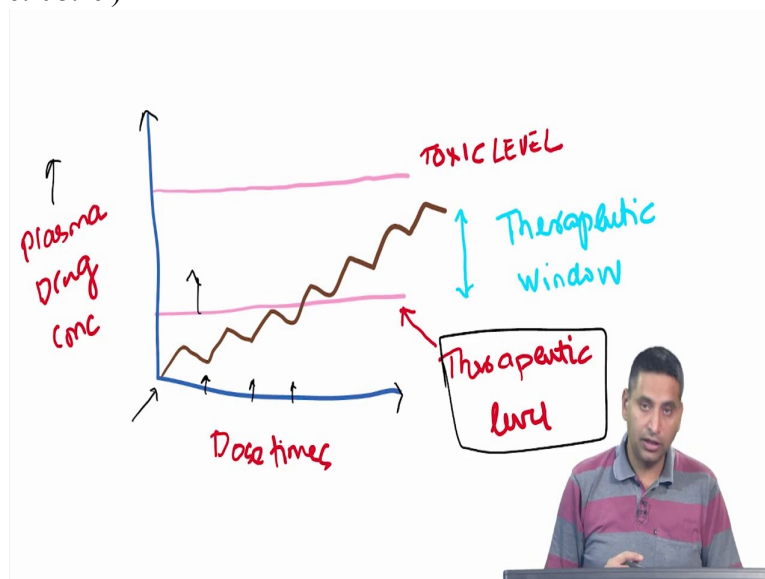
So now there is a concentration of the drug in plasma wherein there is a therapeutic effect,

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Ok. So any concentration above this therapeutic effect that is anything that is above

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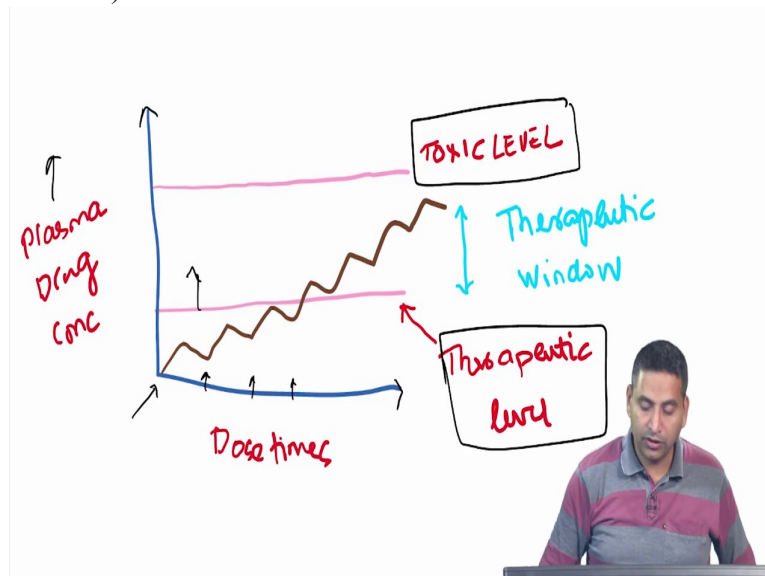


this level, there is going to be therapeutic effect.

So for example if you are taking a drug to address a headache, so there is a dosage at which the headache is going to go down. Any concentration above that is called the therapeutic level.

By the same measure there is also a dose wherein it can achieve toxic levels.

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So most drugs that we take are going to be toxic at high concentrations.

So this top line here is called the toxic level. So the window that is formed between these two levels, that is the therapeutic level and the toxic level is called the therapeutic window.

The larger the therapeutic window, the better it is in terms of how you want to administer a drug. The smaller the therapeutic window the higher the chances that the drug would be toxic and therefore one needs to establish a fairly good therapeutic window if we wish to administer the drug to humans.

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- Explain some of the disadvantages of *in vivo* studies...

The next question is, explain some of the disadvantages of *in vivo* studies.

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In vivo Tests

- *In vivo* tests on animals often involve inducing a clinical condition in the animal to produce **observable symptoms**.
- The animal is then treated to see whether the drug alleviates the problem by eliminating the observable symptoms.
- For example, the development of non-steroidal inflammatory drugs was carried out by inducing inflammation on test animals, then testing drugs to see whether they relieved the inflammation.



So *in vivo* tests are nothing but tests that are conducted on animals. And these animals typically are used

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In vivo Tests

- *In vivo* tests on animals often involve inducing a clinical condition in the animal to produce **observable symptoms**.
- The animal is then treated to see whether the drug alleviates the problem by eliminating the observable symptoms.
- For example, the development of non-steroidal inflammatory drugs was carried out by inducing inflammation on test animals, then testing drugs to see whether they relieved the inflammation.



in such a way that they have observable symptoms. So for example let us say we have an animal which has been induced with cancer.

So now one can use this model to study whether the drug is going to work or not. So if the drug is an anticancer drug and if the size of the tumour goes down then we can study in this animal model whether our molecule is active or not.

In another example if you want to study inflammation and if our non-steroidal anti-inflammatory

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In vivo Tests

- In vivo tests on animals often involve inducing a clinical condition in the animal to produce observable symptoms.
- The animal is then treated to see whether the drug alleviates the problem by eliminating the observable symptoms.
- For example, the development of non-steroidal inflammatory drugs was carried out by inducing inflammation on test animals, then testing drugs to see whether they relieved the inflammation.



drug is going to be, this is anti,

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In vivo Tests

- In vivo tests on animals often involve inducing a clinical condition in the animal to produce observable symptoms.
- The animal is then treated to see whether the drug alleviates the problem by eliminating the observable symptoms.
- For example, the development of non-steroidal inflammatory drugs was carried out by inducing inflammation on test animals, then testing drugs to see whether they relieved the inflammation.



anti-inflammatory drug is going to be useful then we would need to develop a model wherein we induce inflammation on the test animal and then find out whether this molecule has any anti-inflammatory effect.

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- *Transgenic animals* are often used in *in vivo* testing.
- These are animals whose genetic code has been altered.
- For example, it is possible to replace some mouse genes with human genes. The mouse produces the human receptor or enzyme and this allows *in vivo* testing against that target.



Also in *in vivo* studies very frequently transgenic animals are used. These are animals whose genetic code has been altered so that you can use them for better testing.

So for example we can express the human receptor in a mouse. Or you can express the human enzyme in the mouse by altering the genetic code.

Now when we administer a drug we can find out whether the drug acts on the human receptor as it would act on humans or on the human enzyme for example. And it will allow us to test in an animal model before we take it into humans.

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- Alternatively, the mouse's genes could be altered such that the animal becomes susceptible to a particular disease (e.g. breast cancer).
- Drugs can then be tested to see how well they prevent that disease.



Alternatively the mouse genes can also be altered such that the animal becomes more susceptible to a particular disease, for example breast cancer. So then we could test whether the drug will help in preventing that disease.

So here we get a direct readout as to whether the drug can be efficacious in prevention.

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- There are several problems associated with *in vivo* testing.
- It is slow and expensive, and it also causes animal suffering.
- There are the many problems of pharmacokinetics, and so the results obtained may be misleading and difficult to rationalize if *in vivo* tests are carried out in isolation.



Of course one needs to understand that there are several problems associated with *in vivo* testing. A, it is slow, B it is expensive, and it also causes a lot of animal suffering which if we can avoid it would be better.

There are also many problems associated pharmacokinetics. Sometimes the results that we obtain from animal studies can be misleading.

Also if we just do animal studies or *in vivo* tests in isolation, the results that we get may be difficult to rationalize. Because, sometimes the metabolism in animals can be very different from metabolism in humans.

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- For example, a negative result may be due to the drug failing to bind to its target or not reaching the target in the first place?
- Thus, *in vitro* tests are usually carried out first to determine whether a drug interacts with its target, and *in vivo* tests are then carried out to test pharmacokinetic properties.



So for example, a negative result may be due to the drug failing to bind to its target or not reaching the target in the first place. So *in vitro* tests are also carried out to determine whether the drug interacts with its target and then *in vivo* tests are carried out to test the pharmacokinetic properties.

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- Certain *in vivo* tests might turn out to be invalid.
- It is possible that the observed symptoms might be caused by a different physiological mechanism than the one intended.
- For example, many promising anti-ulcer drugs which proved effective in animal testing were ineffective in clinical trials



Certain *in vivo* tests also turn out to be invalid. So if for example the observed symptoms might be caused by a different physiological mechanism than the one intended.

So there are many promising anti-ulcer drugs which have proved very effective in animals but completely ineffective in clinical trials on humans.

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- Different results may be obtained in different animal species. For example, penicillin methyl ester prodrugs are hydrolysed in mice or rats to produce active penicillins, but are not hydrolysed in rabbit, dogs, or humans.



Also there could be different animal species that have different sets of enzymes or drugs. So for example penicillin methyl ester is hydrolyzed in mice or rats to provide active penicillin, but are not hydrolysed in rabbits, dogs or humans.

So here we would be carrying out an experiment in the in vivo model on mice for example and we would find that the active form of penicillin is produced but in reality in humans this may not be effective.

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- What is drug tolerance?



Next question is what is drug tolerance?

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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.



Drug tolerance happens with certain drugs when the effect of the drug diminishes as the number of doses increases. So then to achieve the same effect one needs to take a larger dose of the drug. So this is known as drug tolerance.

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- There are several mechanisms by which drug tolerance can occur.
- For example, the drug can induce the synthesis of metabolic enzymes which result in increased metabolism of the drug.
- Alternatively, the target may adapt to the presence of a drug... Occupancy of a target receptor by an antagonist may induce cellular effects which result in the synthesis of more receptors
- As a result, more drug will be needed in the next dose to antagonize all the receptors



So there are several mechanisms by which drug tolerance can occur and some of them are not very well understood. But one of the ways in which the drug tolerance can happen is if the drug can induce the synthesis of a metabolic enzyme.

So what happens is that once this metabolic enzyme is increased then the drug is going to be metabolized before it gets to its target.

So you need a larger amount of the drug for the same effect. Alternatively the target may adapt. So for example if there is a receptor, the receptor may actually mutate and the binding may not be as effective.

The occupancy of the target receptor by an antagonist may induce cellular effects which result in the synthesis of more receptors.

So now what happens is that instead of having n number of receptors you have $2n$ or $3n$. Therefore you would need a larger amount of the drug to antagonize all the receptor.

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- *Physical dependence* is usually associated with drug tolerance.
- *Physical dependence* is a state in which a patient becomes dependent on the drug in order to feel normal.
- If the drug is withdrawn, uncomfortable **withdrawal symptoms** may arise which can only be alleviated by re-taking the drug.



So drug tolerance is very closely associated with physical dependence. Physical dependence is the state where a patient becomes dependent on the drug in order to feel normal.

And these lead to what are known as withdrawal symptoms.

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- *Physical dependence* is usually associated with drug tolerance.
- Physical dependence is a state in which a patient becomes dependent on the drug in order to feel normal.
- If the drug is withdrawn, uncomfortable withdrawal symptoms may arise which can only be alleviated by re-taking the drug.



So you may have observed a lot of people who smoke have withdrawal symptoms if they do not smoke for a long time.

This is because of the physical dependence that is associated with nicotine.

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- These effects can be explained, in part, by the effects which lead to drug tolerance.
- For example, if cells have synthesized more receptors to counteract the presence of an antagonist, the removal of the antagonist means that the body will have **too many receptors**.
- This results in a 'kickback' effect, where the cell becomes **oversensitive** to the normal neurotransmitter or hormone—this is what produces **withdrawal symptoms**.



And the effects can also be explained by the effects which lead to drug tolerance.

So what happens is that if the cells have synthesized more receptors to counteract the presence of an antagonist then the removal of the antagonist means that the body will have too many receptors.

This results in what is known as a kickback effect where the cells become oversensitive to the normal neurotransmitter. And this is what produces withdrawal symptoms.

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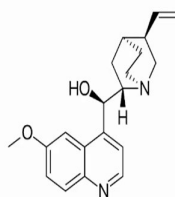
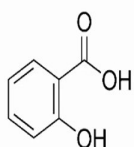
- These will continue until the excess receptors have been broken down by normal cellular mechanisms—a process that may take several days or weeks



So these will continue until the excess receptors have been broken down by normal cellular mechanisms, a process that may take several days or weeks.

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- Salicylic acid is absorbed more effectively from the stomach than from the intestines, whereas quinine is absorbed more effectively from the intestines than from the stomach. Explain these observations. Which compound would you administer orally...

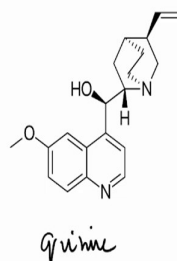
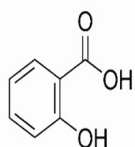


Wikimedia commons

The next question, salicylic acid is absorbed more effectively from the stomach than from the intestines whereas quinine which is shown here

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- Salicylic acid is absorbed more effectively from the stomach than from the intestines, whereas quinine is absorbed more effectively from the intestines than from the stomach. Explain these observations. Which compound would you administer orally...



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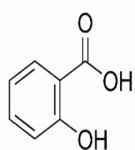


is absorbed more effectively in the intestines. So explain these observations and which compound would you administer orally?

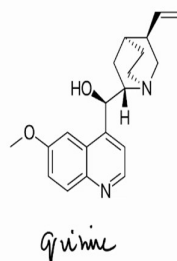
So here is salicylic acid. So

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- Salicylic acid is absorbed more effectively from the stomach than from the intestines, whereas quinine is absorbed more effectively from the intestines than from the stomach. Explain these observations. Which compound would you administer orally...



Salicylic acid

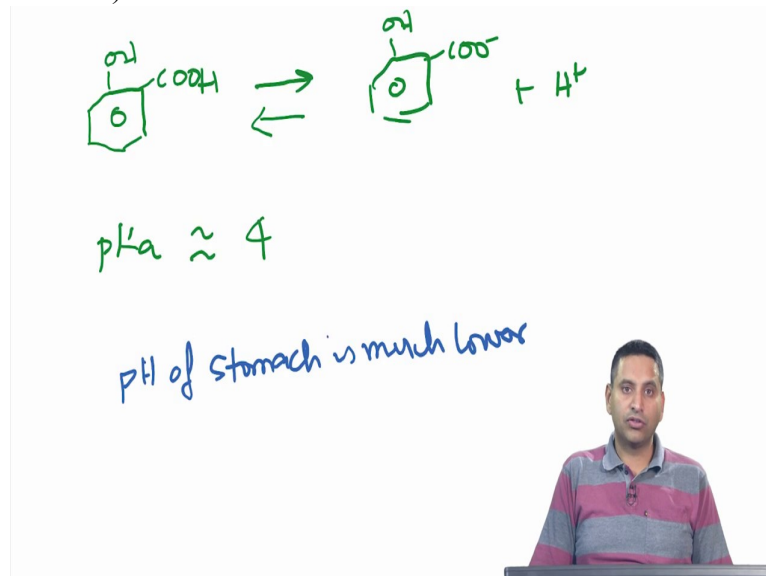


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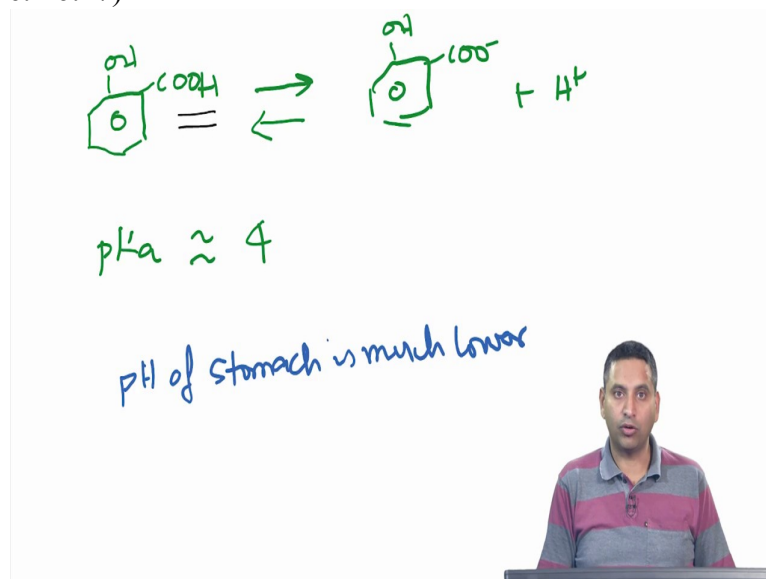
in order to address this question let us now look at some acid based effects.

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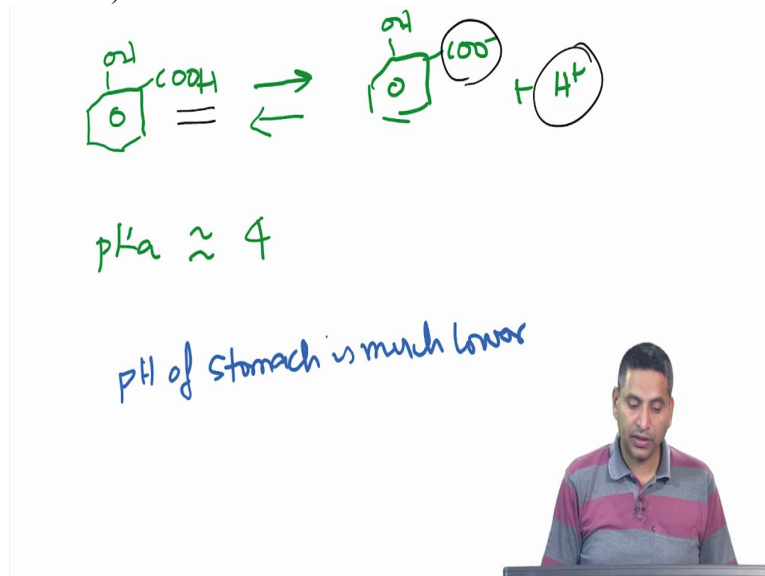
So salicylic acid one would expect that the carboxylic acid would have pKa of around

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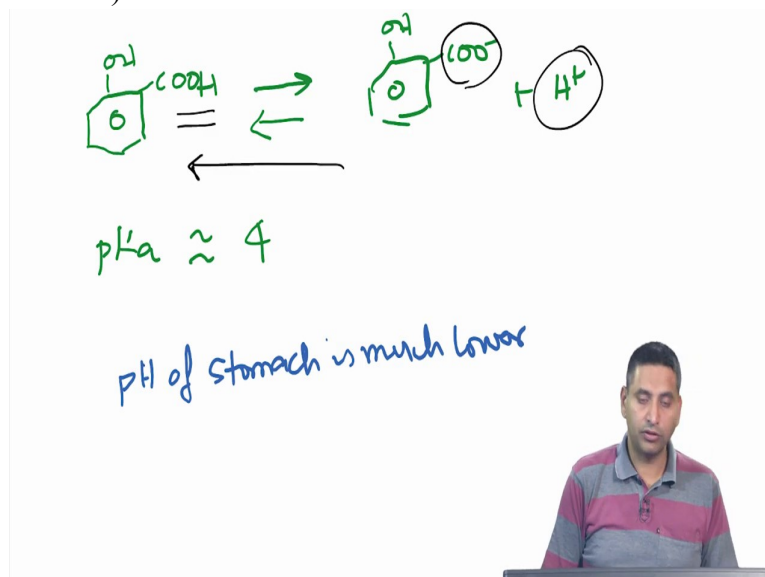
4. And it can ionize and form COO minus and H plus.

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Now the pH of the stomach is significantly lower than this number. So therefore you would expect that this equilibrium would be largely in favor of

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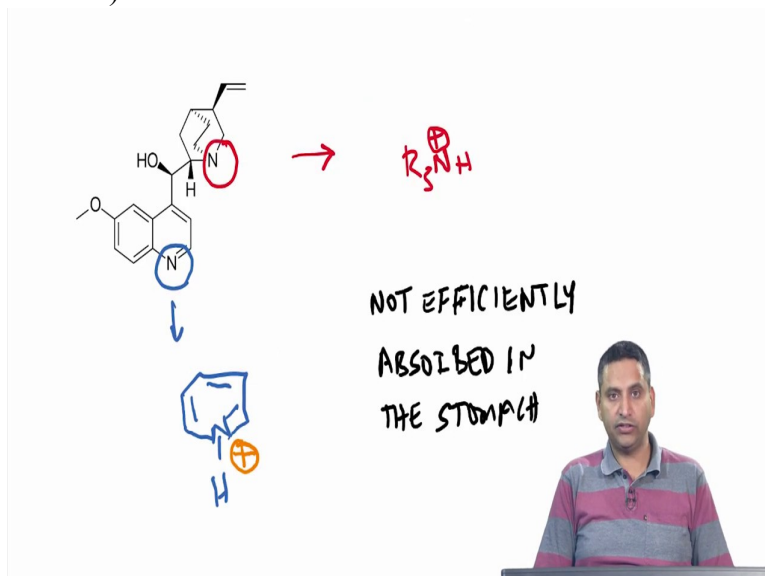


the salicylic acid.

So since salicylic acid is a neutral molecule one would expect that it would be absorbed in the stomach because it can get across the membranes better.

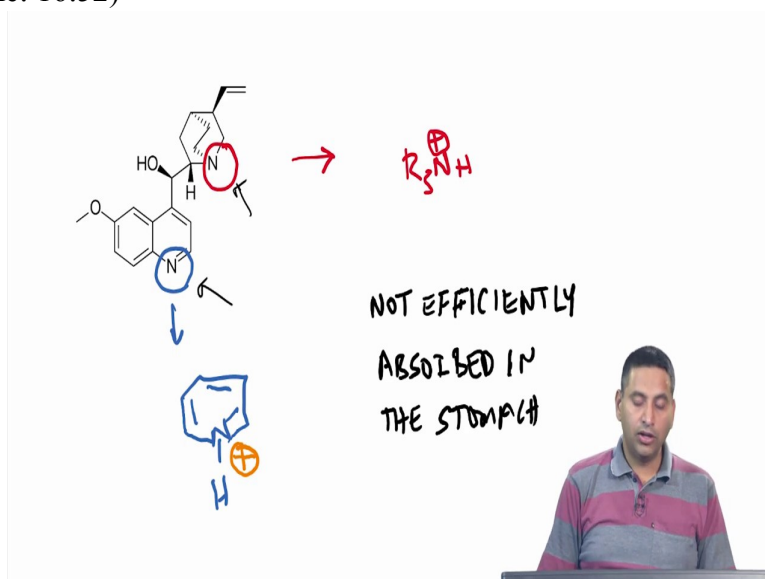
In the second

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case you have two potential centers which can be protonated in low pH. Here is the amine which is here and the pyridine.

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So if the amine gets protonated or the pyridine gets protonated it forms a quaternary ammonium salt.

Now once this salt is formed then it is not efficiently absorbed in the stomach because it does not get across the membrane. Therefore one would expect that it would be efficiently absorbed in the intestine where the pH is substantially higher.

So now one would expect that if salicylic acid is administered it would be better absorbed in the stomach while this quinine would be better absorbed in the intestine.

(Refer Slide Time: 17:25)

- What is meant by target specificity and selectivity? Why is it important?



What is meant by target specificity and selectivity and why is it important?

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- Target specificity and selectivity refers to the ability of a drug to *distinguish between different molecular targets*, whether these targets be totally different in nature or slight variations of the same target. For example, drugs can show specificity or selectivity between different types and subtypes of receptor.
- The ability of a drug to distinguish between different targets is important since it results in a more specific physiological effect, with less side effects



So this is again something that we did in class. So we will repeat it here. Target specificity and selectivity refer to the ability of a drug to distinguish between different molecular targets.


And whether these targets can be totally different in nature or they can be slight variations of the same target. For example drugs can show specificity or selectivity between different types

and subtypes of a receptor. The ability of a drug to distinguish between different targets is very important because it results in a more specific physiological effect with less side effects.

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Target specificity and selectivity

- Antimicrobial agents: targets to choose are those that are unique to the microbe and are not present in humans.
- For example, **penicillin** targets an enzyme involved in bacterial cell wall biosynthesis.
- Mammalian cells do not have a **cell wall**, so this enzyme is absent in human cells and penicillin has few side effects
- Several agents used to treat AIDS inhibit an enzyme called **retroviral reverse transcriptase**, which is unique to infectious agent HIV



Let us look at the case of antimicrobial agents. So antimicrobial agents are, one would want to choose the target that is unique to the microbe but it is not present in the humans.

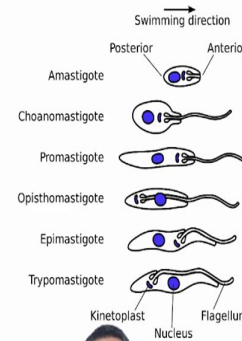
For example penicillin targets an enzyme which is involved in the bacterial cell wall synthesis. Mammalian cells do not have a cell wall. And so this enzyme is absent in human cells. And penicillin has few side effects.

There are also other agents which are used to treat AIDS which is Acquired Immuno Deficiency Syndrome. And these inhibit an enzyme called as retroviral reverse transcriptase.

This enzyme is unique to the infectious agent HIV.

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- Other cellular features that are unique to microorganisms could also be targeted.
- For example, the micro organisms which cause sleeping sickness in Africa are propelled by means of a tail-like structure called a **flagellum**.
- So designing drugs that bind to the proteins making up the flagellum and prevent it from working could be potentially useful in treating that disease



Source: [Wikipedia commons](#)

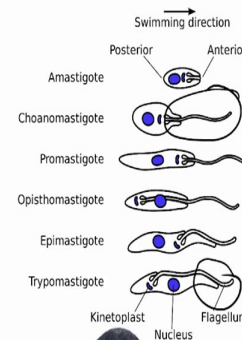


So there are other cellular features that are unique to microorganisms that could also be targeted.

So for example the microbe which causes the sleeping sickness in Africa is propelled by means of a flagellum, Ok.

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- Other cellular features that are unique to microorganisms could also be targeted.
- For example, the micro organisms which cause sleeping sickness in Africa are propelled by means of a tail-like structure called a **flagellum**.
- So designing drugs that bind to the proteins making up the flagellum and prevent it from working could be potentially useful in treating that disease



Source: [Wikipedia commons](#)



So this flagellum is very unique structure and so we can design drugs that binds specifically to proteins making up the flagellum and prevent it from working. And that might be useful in treating the disease.

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- *Fungi have been a richer source of antibacterial agents than bacteria. Suggest why this might be so.*



Fungi have been a richer source of antibacterial agents than bacteria. Suggest why this might be so?

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- *There is a constant battle going on in the microbiological world between different microorganisms. Fungi and bacteria have to compete with each other for available nutrients and if one or the other gains some sort of advantage over the other, it could become dominant and a 'winner takes all' situation may arise.*
- *In general, fungi are slower growing than bacteria which means that bacteria should be more likely to gain dominance. However, many fungi can counteract this disadvantage by producing antibacterial agents which either kill competing bacterial cells or slow down their growth.*
- *This allows fungal cells to compete with bacterial cells on a more even footing for available nutrients.*



So as we described earlier there is a constant battle going on in the microbial world. So there are different microorganisms and these compete for the same space and same resources.

So fungi and bacteria have to compete with each other for available nutrients. And if one gains some sort of advantage then it could result in a dominance and then it could also result in the winner-takes-all situation

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- There is a constant battle going on in the microbiological world between different microorganisms. Fungi and bacteria have to compete with each other for available nutrients and if one or the other gains some sort of advantage over the other, it could become dominant and a 'winner takes all' situation may arise.
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- This allows fungal cells to compete with bacterial cells on a more even footing for available nutrients.



wherein there is only organism that survives.

In general fungi are slower growing than bacteria, which means that bacteria should be more likely to gain dominance because they grow much faster. However many fungi can counteract this disadvantage by producing antibacterial agents which either kill competing bacteria or slowdown their growth.

These compounds allow the fungal cells to compete with bacterial cells on a more even footing for available nutrients.

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- There are significant differences between the cellular structures of fungi and bacteria.
- Fungal cells are eukaryotic and are more complex than the prokaryotic cells of bacteria, and so it is possible for fungi to produce agents which affect features of bacterial cells that are not present in fungal cells.
- Alternatively, antibacterial agents produced by fungal cells may disrupt a biochemical process that takes place in bacterial cells but not in fungal cells. Since fungal cells and mammalian cells are both eukaryotic in nature, there is a good chance that some of these antibacterial agents may be used in medicine without serious side effects



And since there are significant differences between the cellular structure of fungi and bacteria which need attention.

So fungal cells are eukaryotic and more complex than prokaryotic cells or bacteria. So it is possible for fungi to produce agents which affect features of bacterial cells but that are not present in fungal cells. Alternatively antibacterial agents produced by fungal cells may disrupt a biochemical process that takes place specifically in bacteria but not in fungi.

Since fungal cells and mammalian cells are both eukaryotic in nature there is a good chance that some of these antibacterial agents may be used in medicine without serious side effects.

(Refer Slide Time: 21:08)

- A drug has a half-life of 4 hours. How much of the drug remains after 12 hours?



The next question is a drug has a half life of 4 hours. How much of the drug remains after 12 hours?

So in order to answer this question let us start with 100 percent of the drug.

In 4 hours it becomes 50 percent. In

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- A drug has a half-life of 4 hours. How much of the drug remains after 12 hours?

$$100\% \xrightarrow{4h} 50\% -$$



another 4 hours it becomes 50 percent of 50

(Refer Slide Time: 21:29)

- A drug has a half-life of 4 hours. How much of the drug remains after 12 hours?

$$100\% \xrightarrow{4h} 50\% \xrightarrow{4h} 25\%$$



which is 25 percent. In another 4 hours it becomes 12 point 5 percent.

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- A drug has a half-life of 4 hours. How much of the drug remains after 12 hours?

$$100\% \xrightarrow{4h} 50\% \xrightarrow{4h} 25\% \xrightarrow{4h} 12.5\%$$



So 4 plus 4 plus 4 equals to 12 hours, so in 12 hours we would expect 12 point 5

(Refer Slide Time: 21:44)

- A drug has a half-life of 4 hours. How much of the drug remains after 12 hours?

$$100\% \xrightarrow{4h} 50\% \xrightarrow{4h} 25\% \xrightarrow{4h} 12.5\%$$



percent of the drug to remain.

(Refer Slide Time: 21:46)

- *Explain how enhancing a side-effect can be an effective strategy for new drug discovery*



Explain how enhancing a side effect may be an effective strategy for new drug discovery.

So we have looked at several times about how we want to avoid side effects. So here is a very interesting strategy where we want to enhance the side effect.

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- *Enhancing a side effect: Sometimes, a drug is associated with a side-effect that can be useful. This aspect can then be developed further*
- *For example, most sulphonamides have been used as antibacterial agents.*
- *However, some sulphonamides with antibacterial activity could not be used clinically because they had convulsive side effects brought on by hypoglycaemia*



Patrick, G. L.

So enhancing the side effect is usually a strategy that we adopt during clinical trials. So when a drug is found to have a particular side effect then one can use that, or exploit that to develop a new drug. So for example sulphonamides have been used extensively as antibacterial agents.

But there are some sulphonamides which have antibacterial activity but they could not be used because they are associated with convulsive side effects

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- *Enhancing a side effect:* Sometimes, a drug is associated with a side-effect that can be useful. This aspect can then be developed further
- For example, most sulphonamides have been used as antibacterial agents.
- However, some sulphonamides with antibacterial activity could not be used clinically because they had convulsive side effects brought on by hypoglycaemia

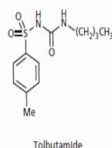


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brought out by hypoglycaemia. Hypoglycaemia is nothing but lowering of blood sugar.

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- But the ability to lower blood glucose levels would be useful in the treatment of diabetes...and to enhance the hypoglycaemic activity.
- This led to the antidiabetic agent *tolbutamide*



Tolbutamide

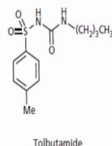


Patrick, G. L.

So the ability to lower blood sugar or blood glucose levels is useful in the treatment of an entirely different disease which is diabetes. So one can now use this method to enhance the hypoglycaemic effect and this strategy led to the development

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- But the ability to lower blood glucose levels would be useful in the treatment of diabetes...and to enhance the hypoglycaemic activity.
- This led to the antidiabetic agent tolbutamide

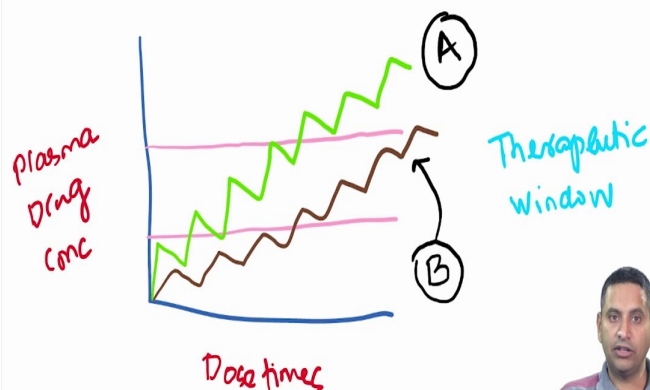


Patrick, G. L.

of tolbutamide which is an antidiabetic drug.

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- Which dosage regimen would you prefer? A or B?

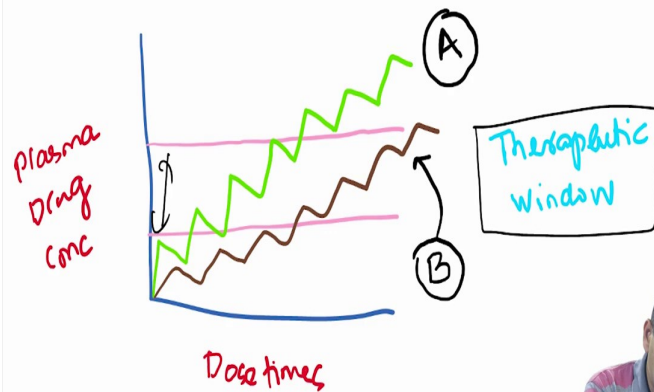


Next question is which dosage regimen would you prefer, A or B?

So this is an interesting question because we have a well-defined therapeutic window which is here.

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- Which dosage regimen would you prefer? A or B?

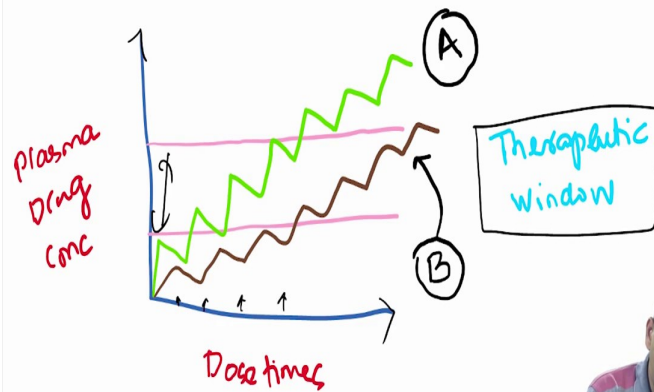


On the y axis is the plasma drug concentration. In the x axis it is dose times.

So here the dose is given, as you can see here is the second dose, here is the

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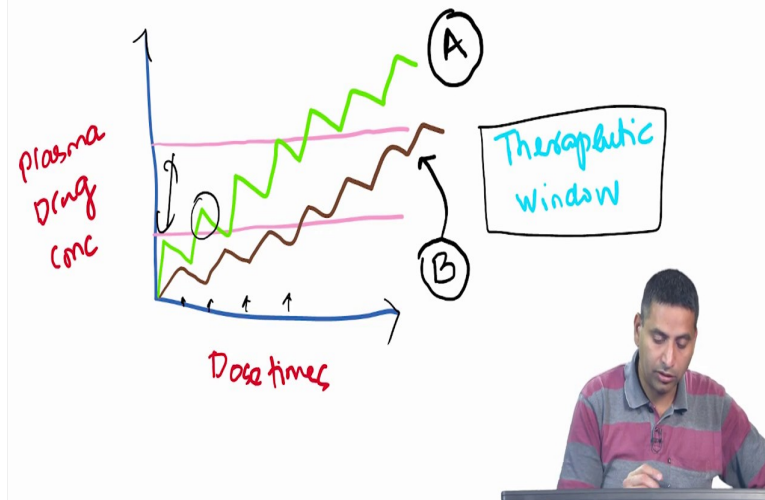
- Which dosage regimen would you prefer? A or B?



third dose, here is the fourth dose, fifth dose and so on. So if we want to have a rapid effect, that means within the third

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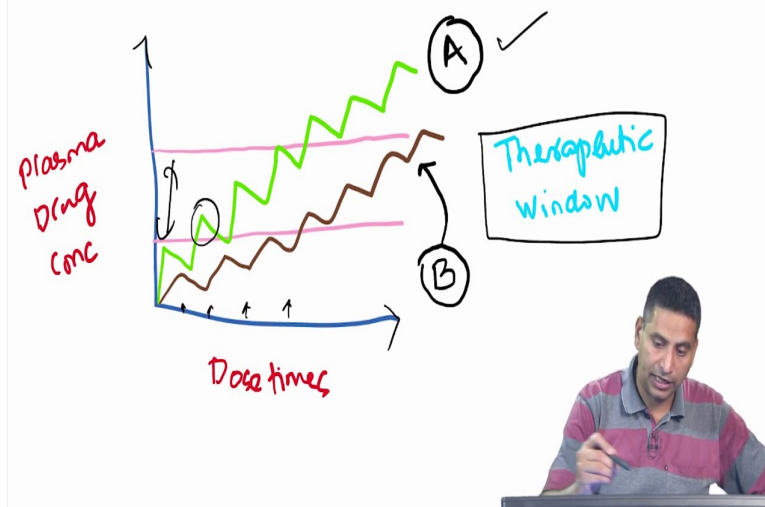
- Which dosage regimen would you prefer? A or B?



or fourth dose you have efficacy then we would prefer A.

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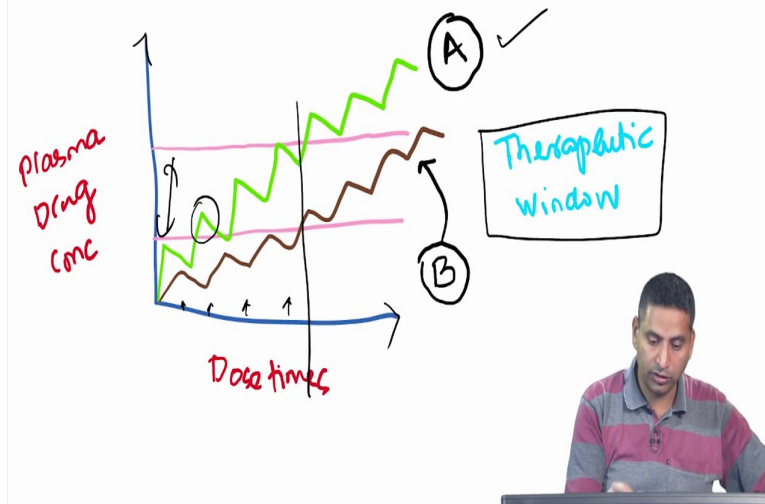
- Which dosage regimen would you prefer? A or B?



But we need to make sure that we do not go

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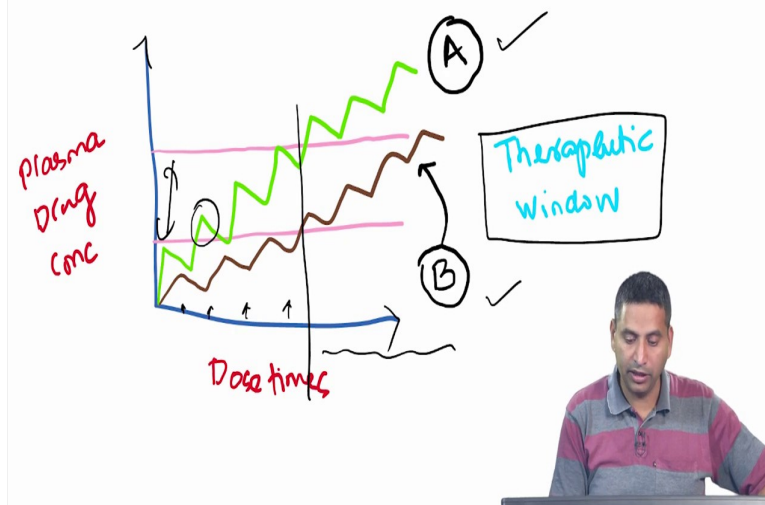
- Which dosage regimen would you prefer? A or B?



beyond this dosage regimen. If we prefer a longer duration of treatment and better efficacy for longer time then we would prefer B

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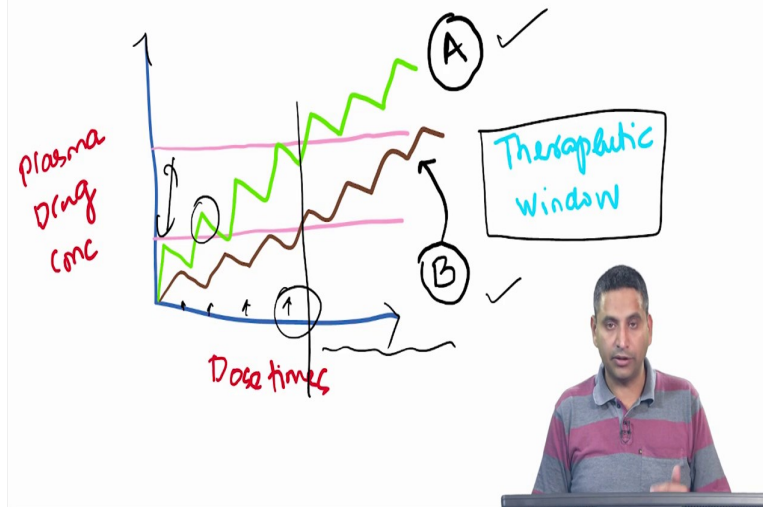
- Which dosage regimen would you prefer? A or B?



because this has a longer therapeutic window, or a broader therapeutic window under which the drug is still efficacious. However the number of doses needed for us to achieve the therapeutic window

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- Which dosage regimen would you prefer? A or B?



is still higher.