Medicinal Chemistry
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Lecture 38 – Tutorial 10
ADME

Welcome to the tutorial session, so today we are going to look at some aspects of ADME. So, ADME is nothing but absorption, distribution, metabolism and excretion so we have been dealing with this concept from the past few lectures and so we will now look at some problems associated with these topics, right.

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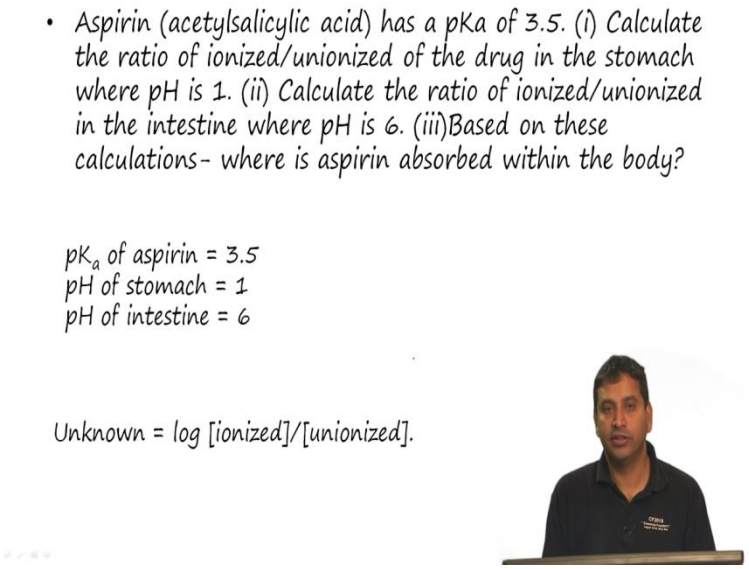

So the first question is, aspirin which is acetyl salicylic acid has a pKa of 3.5 okay. So the first subpart to this question is; calculate the ratio of ionized by unionized of the drug in the stomach where the pH is 1 okay. The second part is, calculate the ratio of ionized by unionized in the intestine where the pH is 6 and based on these calculations can you suggest where aspirin would be absorbed within the body? Okay, so we have been given this data so pKa of aspirin 3.5, pH is 1 in stomach and pH in the intestine is 6, right. So what we need to find out is the log of ionized divided by unionized okay.

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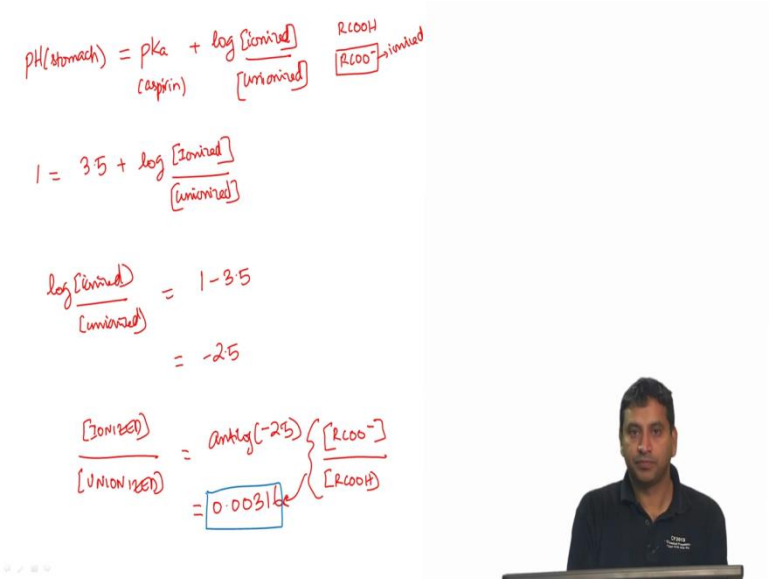

So in order to solve this problem let us now look at the Henderson-Hasselbalch equation which is basically pH of stomach to begin with = pKa of aspirin + log of ionized divided by unionized okay, so this would be the first equation that we would want to write okay. So in the case of salicylic acid we have RCOOH and $RCOO^-$ okay, so the ionized form is $RCOO^-$ and RCOOH is the unionized form. So we have already discussed that pH of stomach is one so this is equal to pKa of aspirin is 3.5 + log of ionized divided by unionized okay, so this is what we would need to find out.

So what we will do is, we will then take 3.5 to the other side. So log of ionized divided by unionized is 1 – 3.5 which is equal to – 2.5 okay. So in order to find this ratio this ratio over here so we would need to take the anti-log so the ratio of ionized by unionized would be antilog of – 2.5 and this value turns out to be 0.00316 okay. So what this number means is that the ratio of $RCOO^-$ divided by ratio of RCOOH is this number okay. So for every thousand unionized molecules right, there are perhaps three ionized molecules okay. So this being such a small number means that the molecule is predominantly in the unionized form. Now let us look at the second part of the question which is to find out the same ratio in the intestine.

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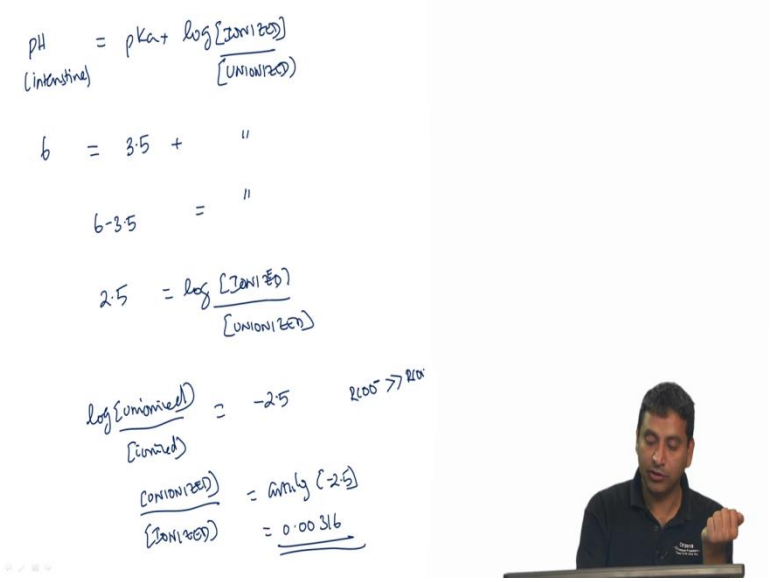

So we have already been given pH of intestine = pKa + log of ionized divided by unionized right, so this is what we know from Henderson–Hasselbalch equation. So again the numbers are pretty straightforward, this is 6 = 3.5 + this value right, so becomes 6 – 3.5 which is 2.5 okay. So in order for us to look at this number so this is basically log of ionized by unionized okay, so if you take the inverse of this number which will be basically log of unionized divided by ionized you get a value of – 2.5 which is exactly identical to what we got in the previous case.

So this value is concentration of unionized divided by ionized = anti log of – 2.5 right, which is nothing but 0.00316 so this is the same number that we got previously except that the numerator and denominator are actually flipped, right. So here there is a larger concentration of ionized molecules that means $RCOO^-$ is significantly greater than RCOOH okay.

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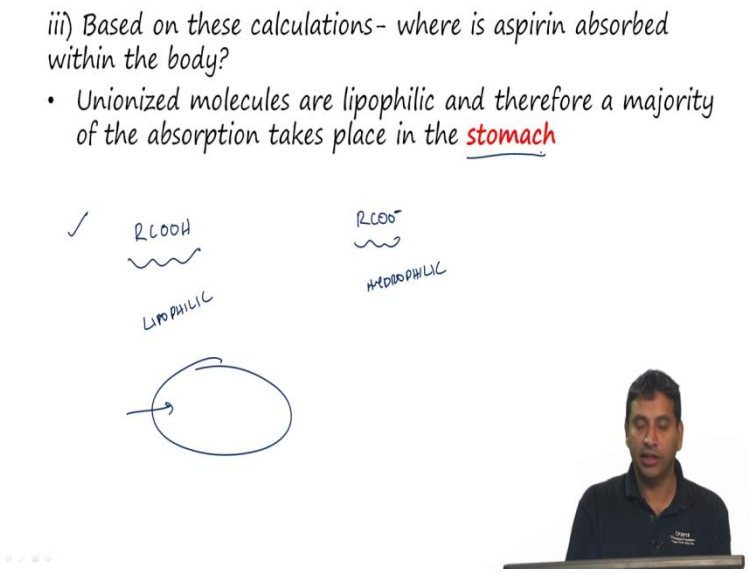

So the next question which is the third part of this question is, basically based on these calculations where is aspirin absorbed within the body. So if you look at the molecule which is basically RCOOH and $RCOO^-$, so this molecule is more lipophilic right and this is more hydrophilic and so what you would expect is that a more lipophilic molecule would get across the cell membrane better and so this molecule should be in predominantly higher amounts. So what we would predict is that since the majority of the molecule is in the unionized form in the stomach, the large amount of this molecule will be absorbed in the stomach and not in the intestine.

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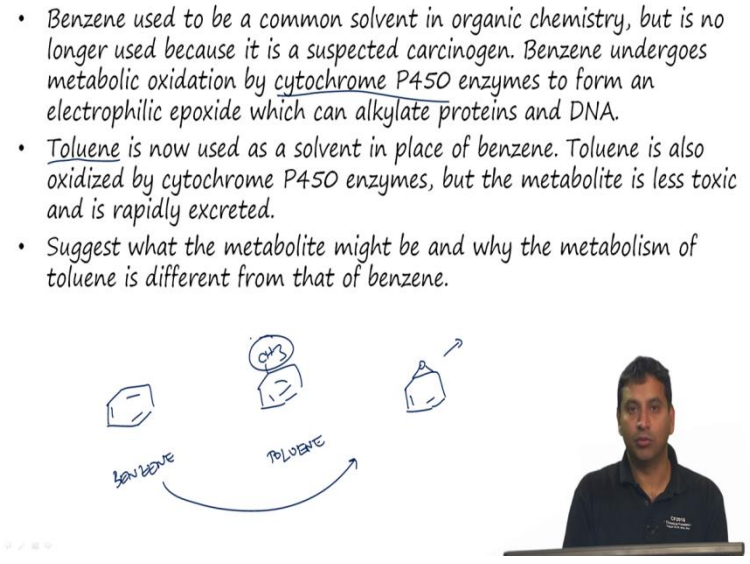

The next question is, benzene used to be a very common solvent in the organic chemistry lab but is no longer used because it is a suspected carcinogen right. So we have already looked at this previously but benzene undergoes metabolic oxidation by P450 enzymes to form an electrophilic epoxide which can alkylate proteins and DNA. Toluene on the other hand is a replacement that is being found and toluene is oxidized by cytochrome P450 but the metabolite is less toxic and rapidly excreted. So the question is, suggest what the metabolite might be and why the metabolism of toluene is different from that of benzene. So in order to address this or answer this question, first let us draw the structure of benzene right, which is over here and toluene which is basically the benzene ring with a methyl group okay.

So benzene as we mention here is going to undergo epoxidation and this can subsequently react with electrophiles okay, this is the reason why benzene is actually a potential carcinogen, but toluene on the other hand is not. So one major difference between benzene toluene is the presence of this methyl group.

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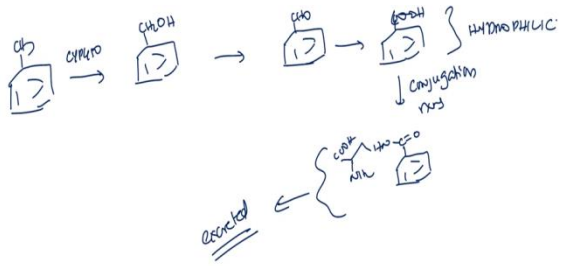

- Benzene gets epoxidized and this can subsequently react as an electrophile
- Toluene is oxidized at the methyl group and is quickly excreted

So toluene can undergo oxidation to form CH_2OH, this is catalysed by CYP-450 which can then subsequently be oxidized further to form an aldehyde which can then again undergo oxidation to form the carboxylic acid okay. And we have already looked at the carboxylic acid can actually react with through conjugation reactions to give perhaps peptides for example, and this is going to be excreted okay. So this itself is hydrophilic and subsequently the carboxylic acid can undergo conjugation to give you more water-soluble derivative which is then quickly excreted. So therefore toluene does not hang out in the body for as much time

as benzene does, where as benzene gets epoxidised and we have already looked at some of the deleterious effects of epoxides.

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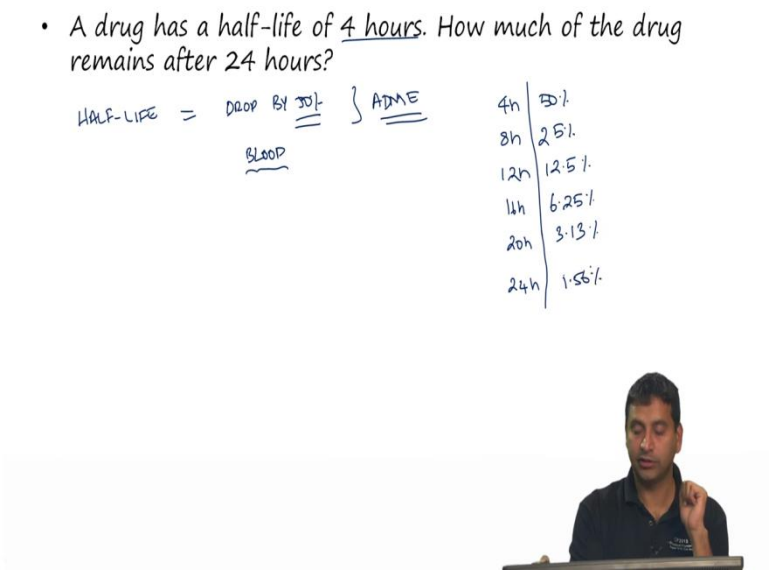

Next question is, a drug has a half life of 4 hours okay, how much of the drug remains after 24 hours. So in order to address this question let us look at half life, basically half life is the time taken for the drug to drop by 50 percent. So this can happen through any of the ADME processes so the absorption can occur, distribution is of course going to occur, metabolism and excretion, so what we are looking at is in the blood right. Now, so the question here is after 4 hours 50 percent remains so let us write that down, 4 hours 50 percent which means that in another 8 hours 50 percent of this number would go down which means that you would have 25 percent still remain okay and in another 4 hours which is 12 hours you could again imagine you could expect another 50 percent of this 25 percent would be gone so you will have 12.5 percent.

And in another 4 hours you will go to 16 hours where this number will go down to 6.25 percent which is exactly half of 12.5 percent and in 20 hours it will further go down to 3.13 percent, so 24 hours it will go down to 1.56 percent.

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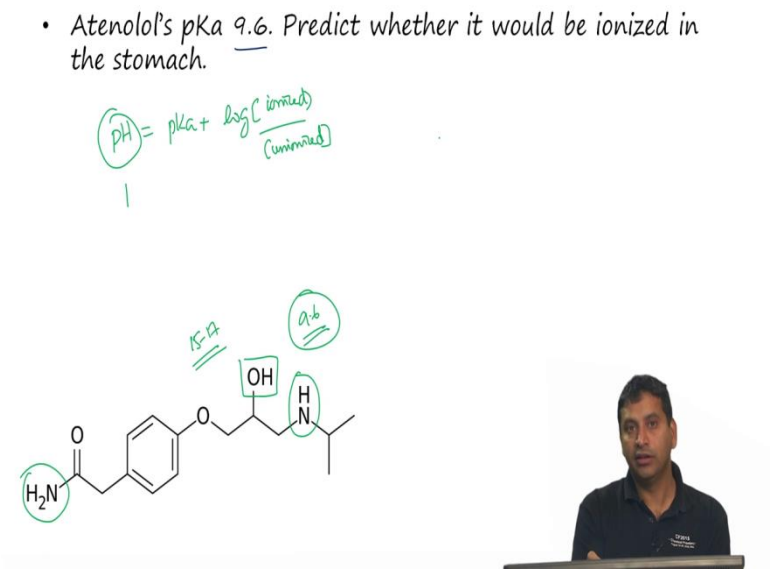

Next question is, atenolol's pKa is 9.6, so question is predict whether it will be ionized in the stomach right. So in order to address this question what we would need to do is to look at the structure very closely and see what are the functional groups which are going to be acidic or basic. So when you are looking at bases, we have already seen that it is basically it is the pKa of the protonated amine, so between an amide and a secondary amine, the amine would have would be a better base okay so therefore the pKa of this amine is expected to be 9.6 rather than the amide okay.

Now we have already seen that the pKa of alcohol is substantially higher somewhere between 15 to 17 and so this would be not this would not be the species that is going to get protonated or deprotonated, so the question is whether this is going to be ionized in the stomach. So we have already looked at pH = pKa + log of ionized by unionized right, so since the pKa is 9.6, we would expect that substantial portion of this molecule is going to be in the protonated state because this number pH of 1 is much greater is much more acidic and therefore it would be ionized in the stomach.

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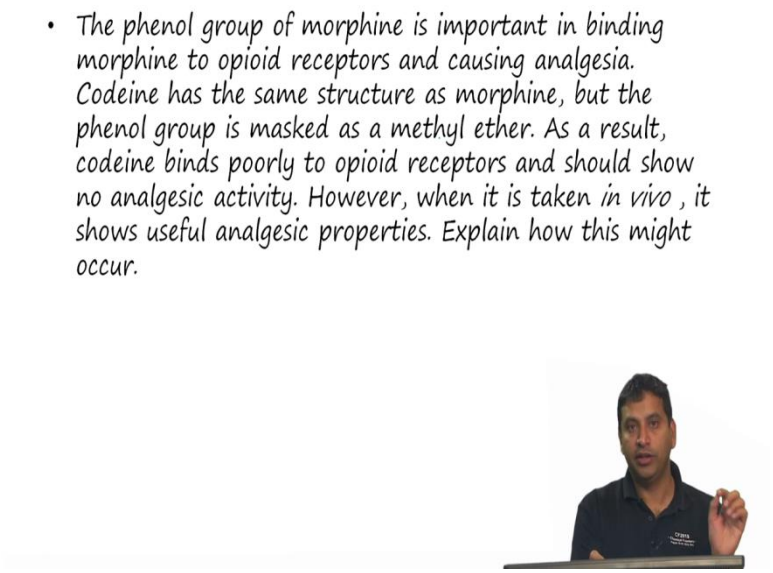

The phenol group of morphine is important in binding to the opioid receptors and this causes analgesia. Codeine which has the same structure as morphine, but the phenol group is masked as masked as a methyl ether, so the phenol of morphine is actually masked as a OMe. As a result, codeine binding binds poorly to opioid receptors and should show no analgesic activity. However, when it is taken in vivo, it shows very useful analgesic properties, so question is explain how this might occur. So in order to address this question so what we are looking at here is this is morphine, the phenol of morphine and this is codeine, and so if you want to understand this point we will have to look at how this molecule is actually going to be metabolized.

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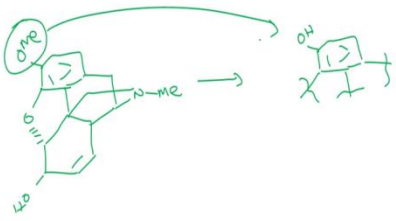

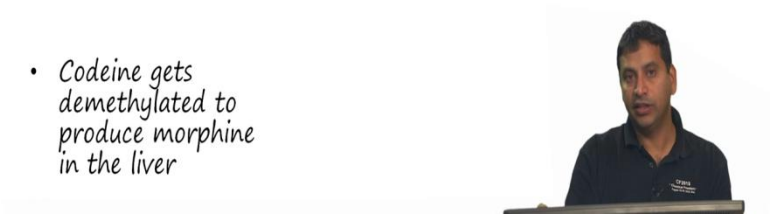

So let us draw the structure of codeine, so this is the structure of codeine OMe, okay so here is the methyl group or methoxy group that we are talking about. So what we would expect is that this methoxy group is going to be metabolized in the liver to produce the corresponding phenol which is basically morphine, right. So I am not drawing out the rest of the molecule but you can imagine that this can occur in the liver and therefore codeine is actually demethylated and therefore it is going to produce the active ingredient which is morphine.

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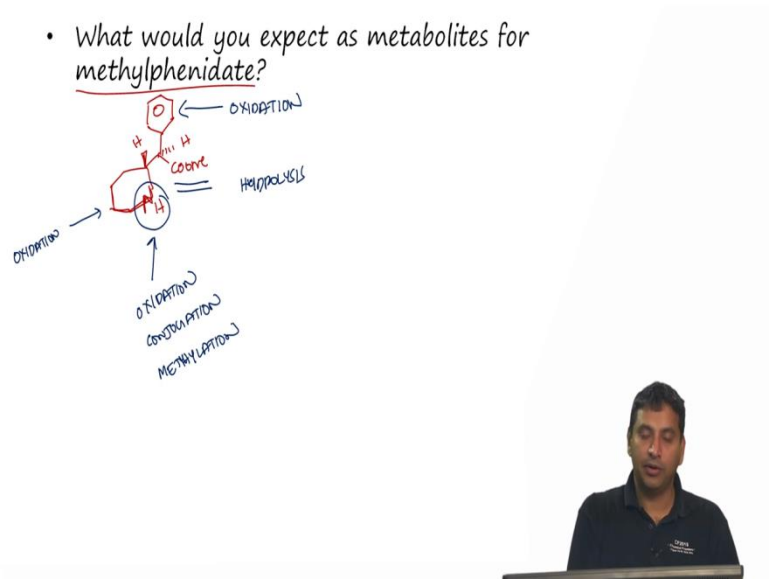

Next question is, what would you expect as metabolites for methylphenidate okay? So methylphenidate has the following structure, so it has a piperazine ring, stereochemistry is over here and going up and it has a benzene ring, and it has a COOMe and a hydrogen okay, so this is the structure of methylphenidate okay. So by looking at this molecule we can see that it has a number of functional groups that can be metabolized okay. So we have already looked at the possibility of the phenol ring getting oxidized so you could have oxidation over here okay, you can also have on the carbocycle or the heterocycle, you have CH_2's which are exposed and these again can undergo oxidation okay.

And we have already looked at that the nitrogen NH can undergo oxidation and this ester can undergo hydrolysis okay, so these are some of the important reactions of oxidation of hydrolysis but in addition, this NH can also undergo conjugation okay, so we have already looked at the possibility of conjugation with glucoronic acid with amines and lastly it can also undergo methylation okay, so these are the major reactions that we would expect with this molecule. So to draw out some of the metabolite let us draw the structure of this molecule once again.

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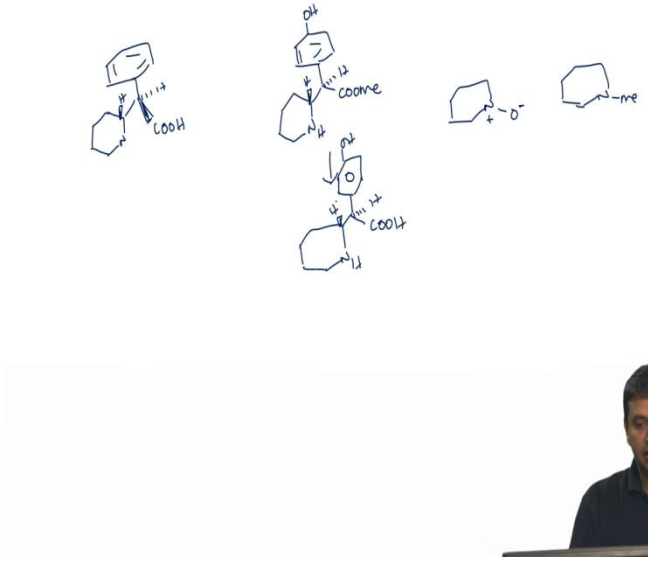

So for example if the ester is undergoing hydrolysis, you will end up with COOH and the rest of the molecule remains the same okay. And if you think if you suspect that the benzene ring is going to be oxidized, what might happen is that the benzene ring is going to form an epoxide, which can then do a hydride shift to give you a phenol, and we have already seen that the phenol formation is going to be favoured in the *para*-position when you have a substituent, so this remains rest of the molecule remains the same okay. You could also have as we discussed oxidation at the nitrogen position, so I am not going to draw out the rest of the molecule but you could have *N*-oxide being formed.

We could also have methylation which is shown over here right, and lastly we can also have conjugation with other things which are not glucoronic acid which I am not showing, but you could also have multiple things happening in the same molecule. So for example, if this undergoes ester hydrolysis then you would generate the phenol remains the same but this will form COOH, H, the stereo centre perhaps remains the same okay. So what we would expect during metabolism of this drug is some of these products.

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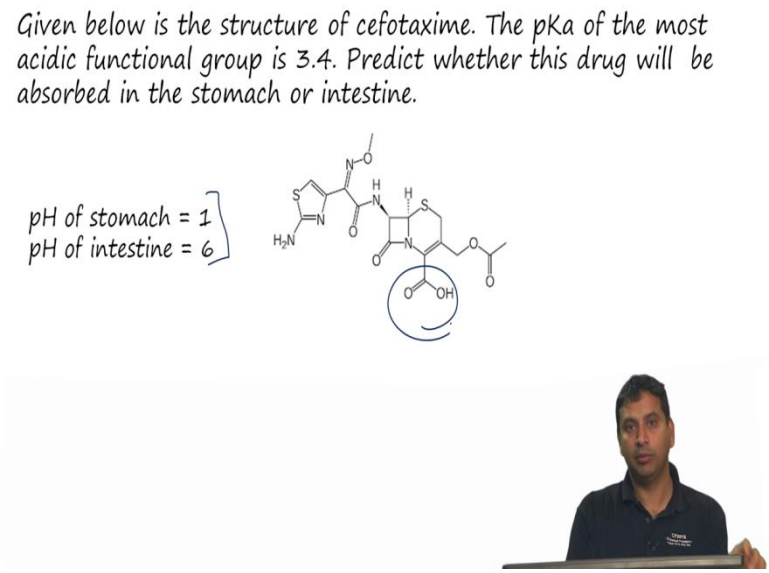

So next question is, given below is the structure of cefotaxime which is an antibiotic, the pKa of the most acidic functional group is 3.4 okay. Question is, predict whether this drug will be absorbed in the stomach or in the intestine. So we have already looked at the pH of stomach to be 1 and the pH of intestine to be around 6 okay, so the pKa of this molecule is 3.4 and we would expect that this carboxylic acid would be the most acidic functional group and therefore the pKa of this functional group would be 3.4 okay.

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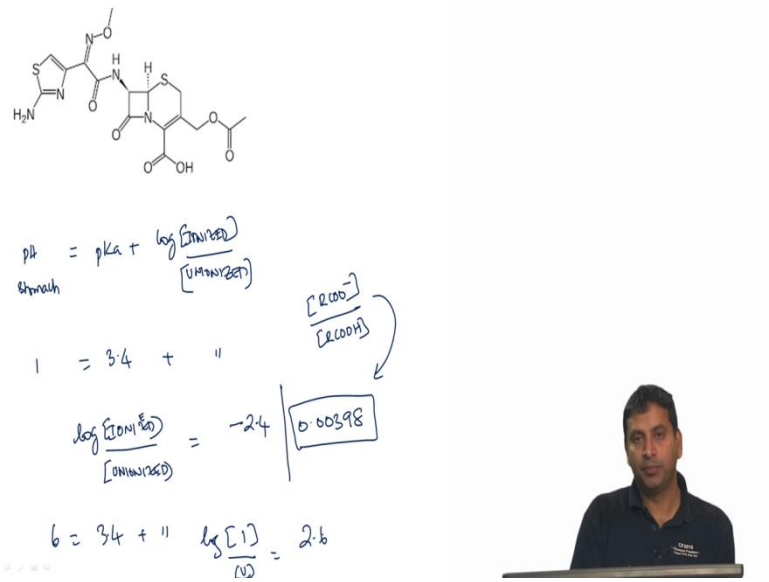

Now let us go through the same calculation, so pH of the stomach = pKa of the drug + log of ionized by unionized right, so this is the same drill that we have done earlier so I am going to skip some steps so that we do not have to repeat the whole thing but you can do 1 = 3.4 + this

number and so if you take log of the ionized divided by unionized right, so this will be – 2.4 which is going to give you if we take anti-log of this number you are going to get 0.00398 okay, so this would be the concentration of ionized divided by unionized that means $RCOO^-$ divided by RCOOH okay. So this number being extremely small you can imagine that predominantly the molecule is going to be in the unionized form.

So we have already seen that once the molecule is in the unionized form, it can get across membranes better and so one would predict that in this pH the molecule is going to be absorbed quite well. If you repeat the same calculation for the intestine you will get 6 = .4 + this log value and so the log value would be ionized divided by unionized would be 6 – 3.4, which would be 2.6 okay. So 2.6 being a positive number, what you would expect is that this is going to be a very large positive value, which means that in the pH of 6 it is going to be in the carboxylate form that is perhaps going to be detrimental for it to be absorbed. Predict whether it is going to be absorbed in the stomach or in the intestine, based on these calculations we will predict that it will be absorbed in the stomach.

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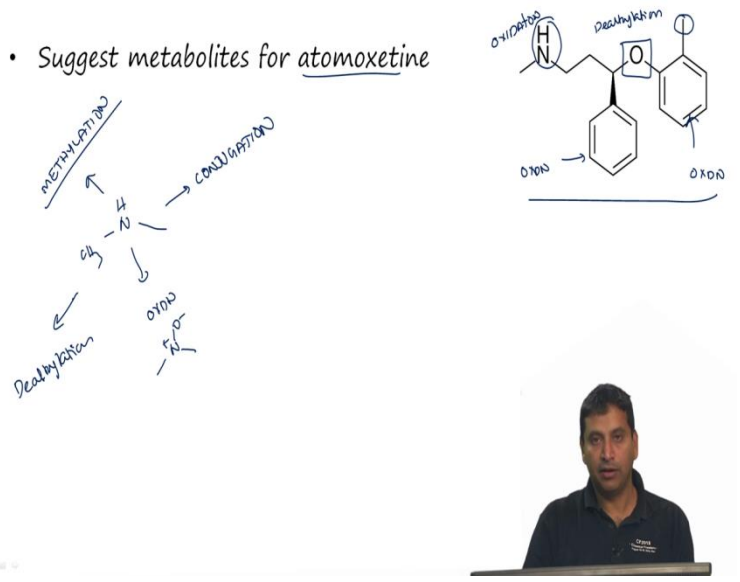

The next question is, suggest the metabolite for atomoxetine okay, so this is the molecule over here and here is the structure of this molecule and again we would be able to suggest that some of the functional groups that can be playing a role here is the amine, so the amine can undergo oxidation right, and we have already seen that the benzene rings can undergo oxidation right. And we have also looked at the toluene position which is going to be susceptible to oxidation and ethers have been shown to be dealkylated under these conditions so this is also a possibility, so this is the deakylation which means that it is going to form a

phenol on one side and you could also have a situation where this NHMe is going to be an important functional group, so let us draw out this NHMe separately.

So NHMe can undergo dealkylation so the methyl group can be removed, you could also have oxidation so you will have *N*-oxides being formed right or it is going to get further oxidized, then you could have conjugations that could occur and lastly you could also have methylation okay. So amines are really important functional groups in many drugs but there are number of metabolic transformations that could occur and so it is sometimes difficult to predict which one is going to have preference over the other.

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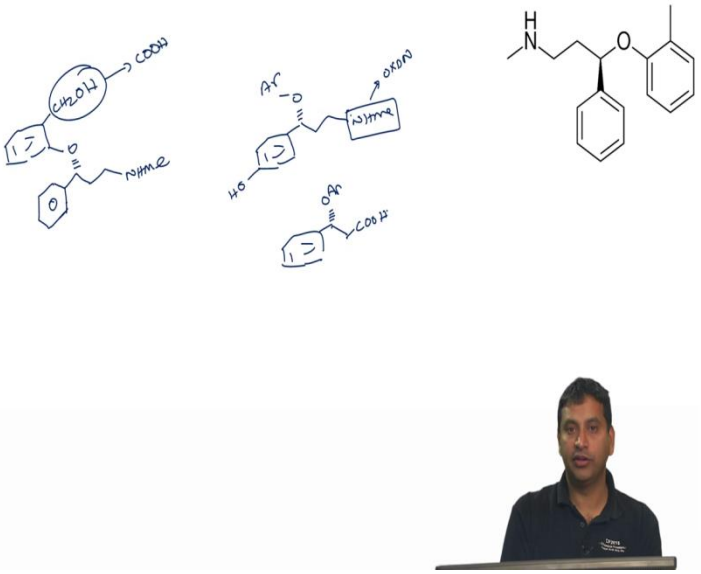

So the major metabolites that we would look at are the toluene ring being oxidized so you will get CH_2OH and this is going to happen perhaps very easily NHMe and this can get further oxidized to give you the carboxylic acid eventually. You could also have the benzene ring undergoing oxidation by monooxygenases to give you the corresponding phenol and as we have already looked it is going to go to the *para*-position and you can also have this NHMe being further metabolized and you could also have oxidation followed by the formation of aldehyde which can then further undergo oxidation to give you the carboxylic acid. So you will have this group undergoing oxidation followed by you will form the aldehyde which can then undergo further oxidation to give you the carboxylic acid. So these are some of the major metabolites that we would expect with this drug.

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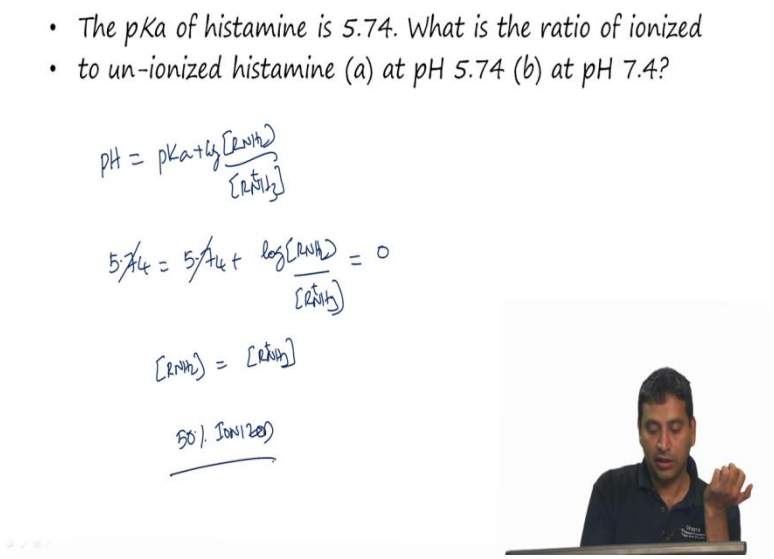

The pKa of histamine is 5.74, what is the ratio of ionized to unionized histamine at pH 5.74 and at pH 7.4 okay, so try to address this question is to look at the Henderson–Hasselbalch equation which is pH = pKa + log of concentration RNH_2 divided by RNH_3^+ okay. So is pH = pKa then you get 5.74 = 5.74 + log of RNH_2 divided by RNH_3^+ so this term can be cancelled so this value = 0 and when this value = 0, the concentration of RNH_2 = concentration of RNH_3^+, which means that it is 50 percent ionized.

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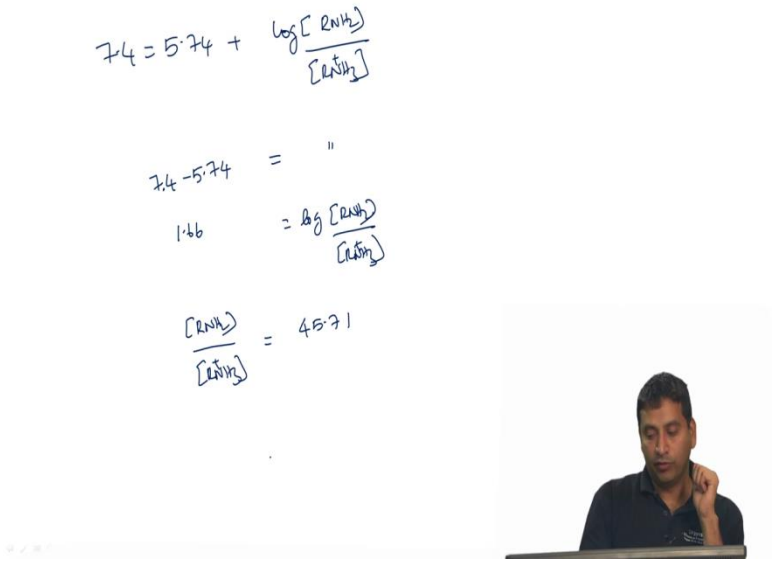

For the same situation in pH 7.4, so you get 7.4 = 5.74 + log of concentration of RNH_2 divided by concentration of RNH_3^+ and so if you take the 5.74 that side, this term becomes

7.4 – 5.74, this value is 1.66 = log of RNH_2 divided by RNH_3^+, so if you take the antilog of this number, you get the concentration of RNH_2 divided by concentration of RNH_3^+ = 45.71 okay.

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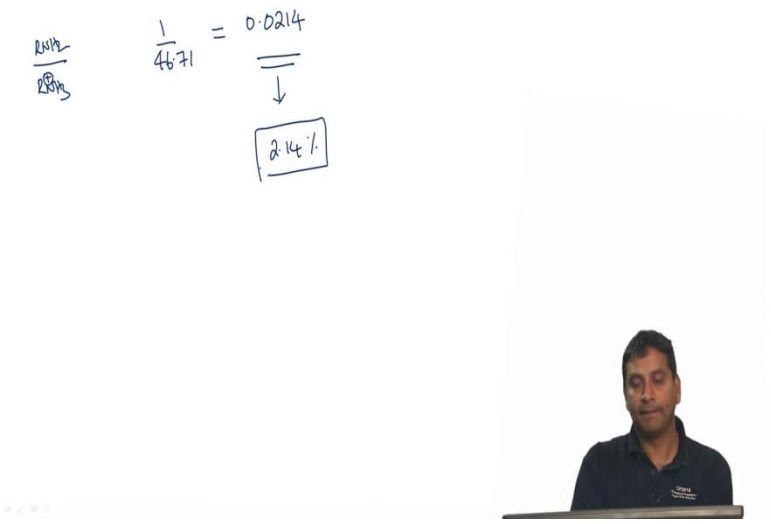

So from this number of what we would conclude is that you have 1 divided by 46.71 is the ratio of RNH_2 divided by RNH_3^+ so 1 divided by 46.71 is nothing but 0.0214, this translates to 2.14 percent. So at pH 7.4 we would expect that 2.14 percent of this molecule would be in the unionized form.

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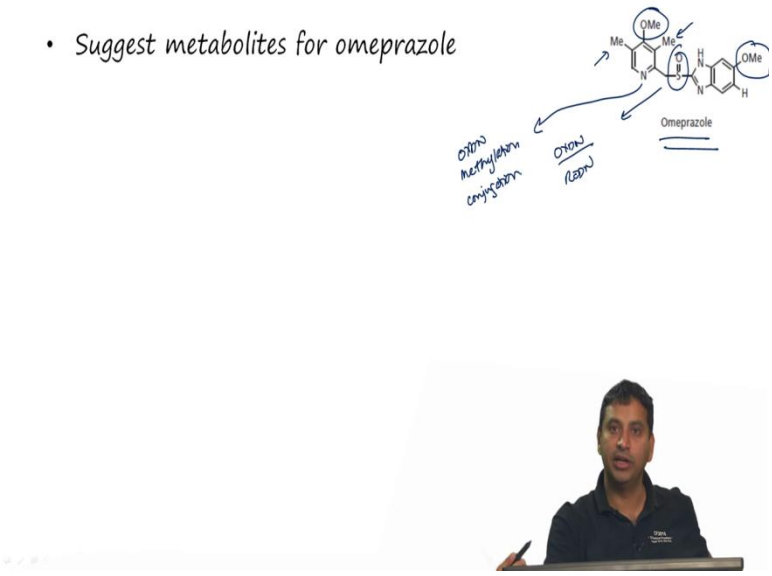

The next question is, suggest metabolites for omeprazole okay. So omeprazole has the following structure as shown here and again it could have a number of things that would happen to this molecule, so now let us look at this in little bit more detail but what we would expect is that it has a OMe group, so OMe can undergo demethylation right and you have this methyl group here which can undergo oxidation, this methyl group here which is identical can also undergo oxidation, so S double bond O can undergo oxidation reduction depending on situation and the benzene ring and the pyridine ring can be oxidized.

The pyridine ring of course because it has a free nitrogen over here or a nitrogen hetero atom here can do a number of things, it can undergo oxidation, it can undergo methylation and we have already looked at that methylation of pyridine ring substantially increase the polarity and it can also undergo conjugation, so these are the major aspects of what a pyridine ring can do, and so with this in mind let us look at the metabolites for omeprazole.

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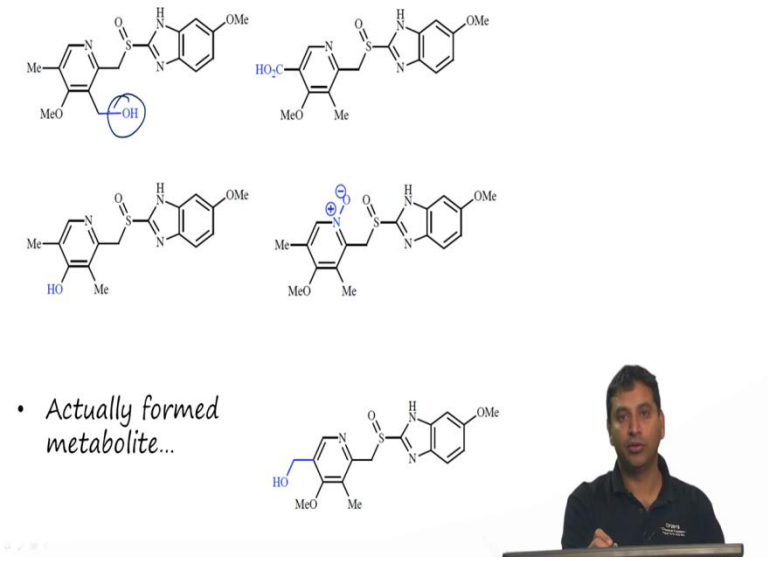

So we would have this CH_3 undergoing oxidation to form CH_2OH, you have the formation of *N*-oxides which is possible and this CH_2OH can further undergo oxidation to form carboxylic acid. And you have the demethylation of the OMe to give you OH and one of the metabolites that actually is form is shown here which is the one with the CH_2OH.

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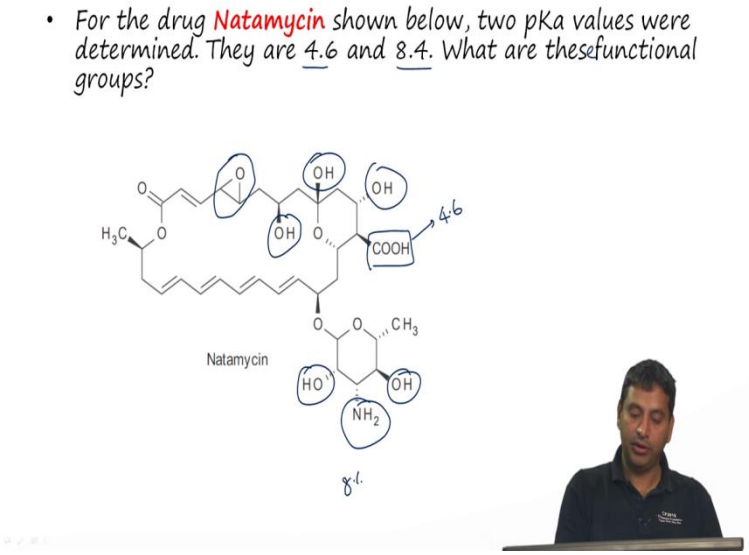

Next question is, for the drug Natamycin shown below, two pKa values were determined and they are 4.6 and 8.4. What are these functional groups is the question. So let us look at this molecule in a little bit of detail, so you have a number of functional groups here, let us look at one by one, you have any epoxide, you have an OH, so epoxide does not have any ionizable or this lone pair is not going to be a very good base. You have the hydroxyl group whose pKa is well into the 14-15 range, similarly this OH is going to be all these hydroxyl groups are going to be similar okay. And I do not see any other way any other functional group here which is going to have pKa less than 10.

Now you have a carboxylic acid, and carboxylic acid as we know have pKa in the range of 4 to 6 and so this could be the one with the pKa of 4.6 and the amine here that is the protonated amine is going to be a good acid, and so the protonated amine the pKa is going to be 8.4 okay.

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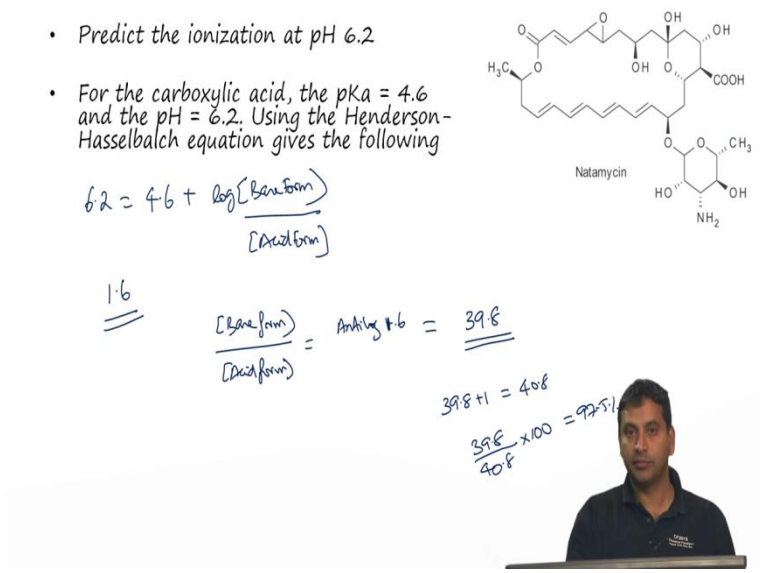

So the next question is, predict the ionization at pH 6.2. So for the carboxylic acid we will use the pKa of 4.6 and the pH is 6.2 so we will use Henderson Hasselbalch equation. So 6.2 = 4.6 + log of the base form divided by the acid form okay, so if you look at this, this value turns out to be 1.6 and then if I take the antilog after this, the concentration of base form by acid form would be the antilog of 1.6 which turns out to be 39.8 okay. So in order to calculate the percent value, what we would do is we would take the total amount would be 39.8 + 1 that is equal to 40.8 so the percent of the base form would be 39.8 divided by 40.8 times 100 which is equal to 97.5 percent.

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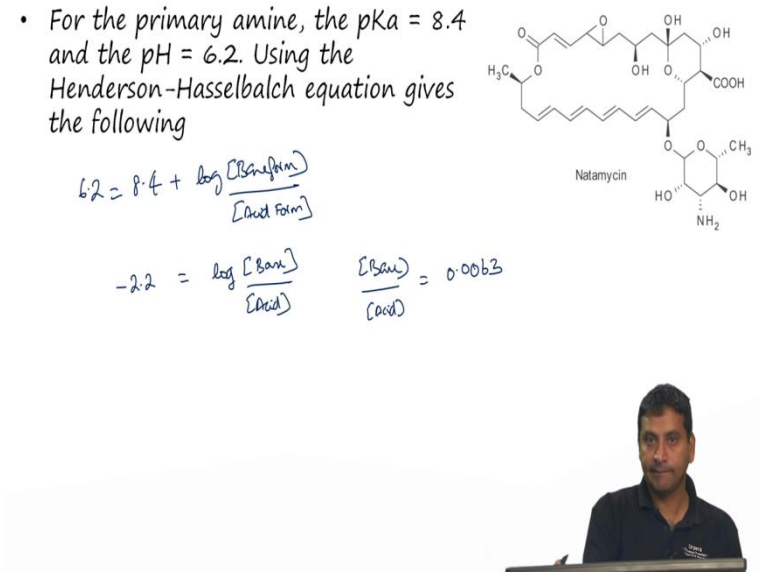

For the primary amine, the pKa is 8.4 and using the Henderson–Hasselbalch equation we get the following equation; 6.2 = 8.4 + log of base form divided by acid form okay. So now if you look at this number you get the value of 6.2 – 8.4 which is basically – 2.2 that is nothing but the log of base divided by acid okay. And so if we take the antilog of this number, you get the concentration of base by acid to be 0.0063 okay.

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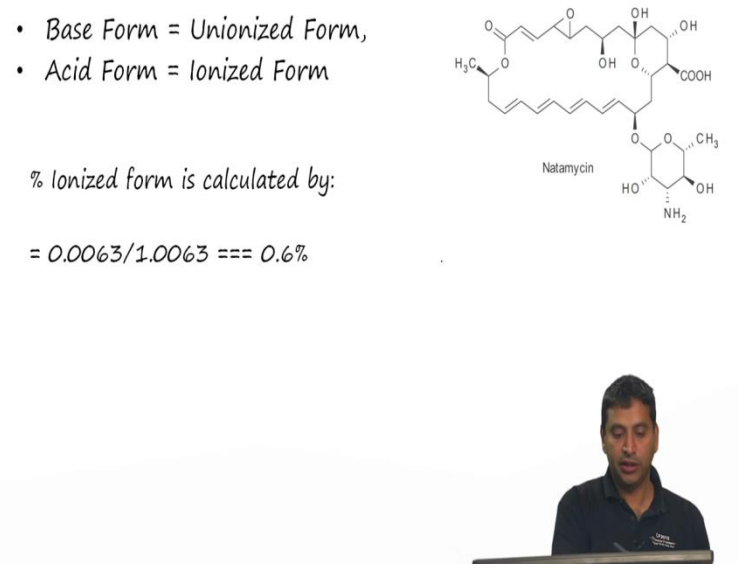

So now if you want to calculate the percent then you do 0.0063 divided by 1.0063 which is nothing but 0.6 percent.

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Next question is, do all phase 2 metabolic reactions result in increased polarity or water solubility? So as we frequently discussed this in the previous lectures, phase 1 and phase 2 metabolism, the common theme is that there is going to be increased polarity so you have oxidation reactions wherein benzene ring becomes a phenol, you have oxidation reaction where a methyl group becomes an alcohol, you also have further oxidation reactions wherer it can form a carboxylic acid. And in phase 2 we have looked at conjugation with glutathione which is going to make it more polar, there is conjugation with glucoronic acid which is again going to make it more polar and so on and so forth.

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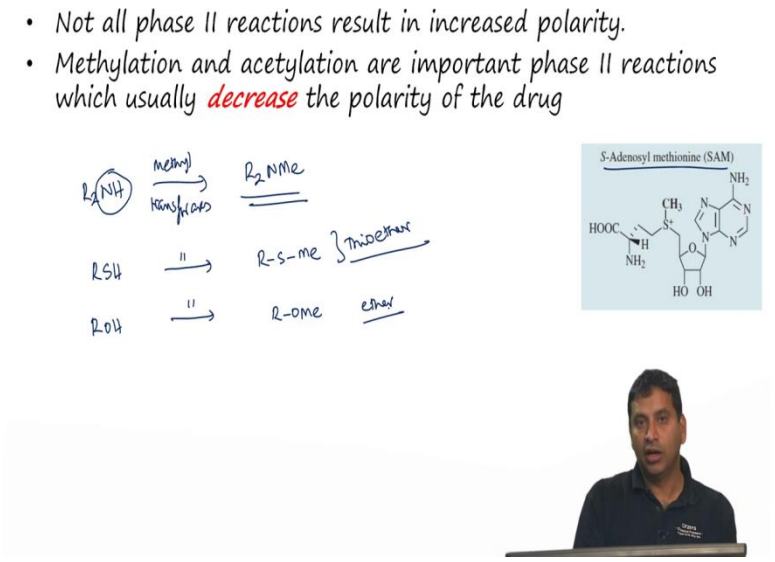

So all these are going to increase the polarity, but not all phase 2 metabolism reactions increase in polarity. So the example that we looked at is methylation okay, so when you have an amine such as R_2NH then there are Methyl transferases which then converts this to R_2NMe okay. So this reaction actually decreases the priority because previously you had the possibility of NH being polar, whereas here you have substituted the hydrogen with methyl and you are declaring the polarity. And we have already looked at that this is mediated by this molecule called as SAM which is S-adenosylmethionine.

The other possibility is thiols undergoing the same reaction to give you to give you RSMe which is basically a thioether okay, and thioether is significantly less polar compared to a thiol. Lastly, you also have the same transformation that could occur with alcohols and it will form an ether, methyl ether which is going to again increase the polarity. So the answer is, not all reactions in phase 1 and phase 2 are going to increase the polarity.

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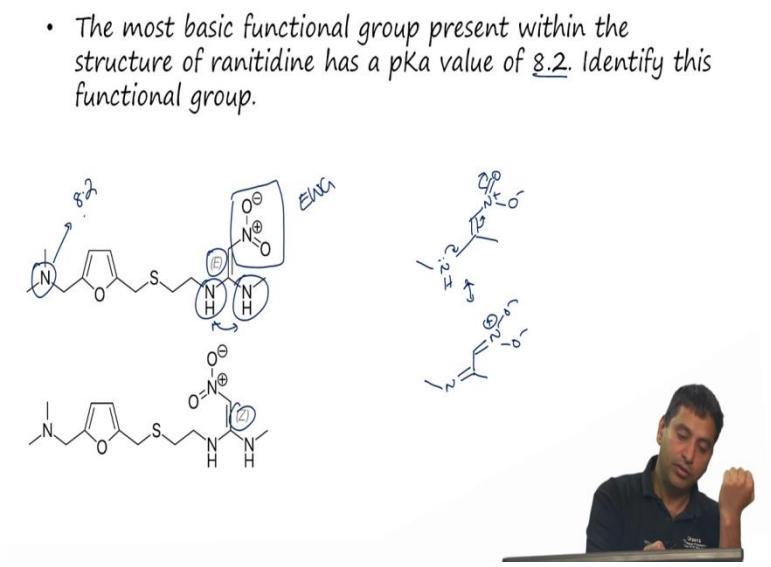

The next question, we are going to deal with this drug called as ranitidine. So the most basic functional group present within the structure of ranitidine has a pKa of 8.2, question is identified this functional group. So in order to, let us look at this molecule, this exists in two stereo isomers Z and E okay, so that is not going to perhaps play a huge role in the pKa values but you have 3 amines centers which we will circle over here and with all other things are equal then these 2 amines would have very similar pKa values, they should be comparable to the other amine.

But since we have an electron withdrawing group attached to this amine, the lone pair on the nitrogen becomes significantly less available, so if we were to draw this structure in the following manner you can draw a resonance form where in this is going to go here and you have N double bond N,O^-,O^-,+ okay, rest of the molecule is being the same. So therefore the lone pair is not really available for it to be donated so we would predict that this nitrogen would have the pKa of 8.2.

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The next question is, calculate the pH that is necessary for this functional group to be 10 percent ionised, 50 percent ionised, 90 percent ionised and 95 percent ionized okay. So again we need to look at pH = pKa + log of base by acid, so we will use this as the basis for our calculations.

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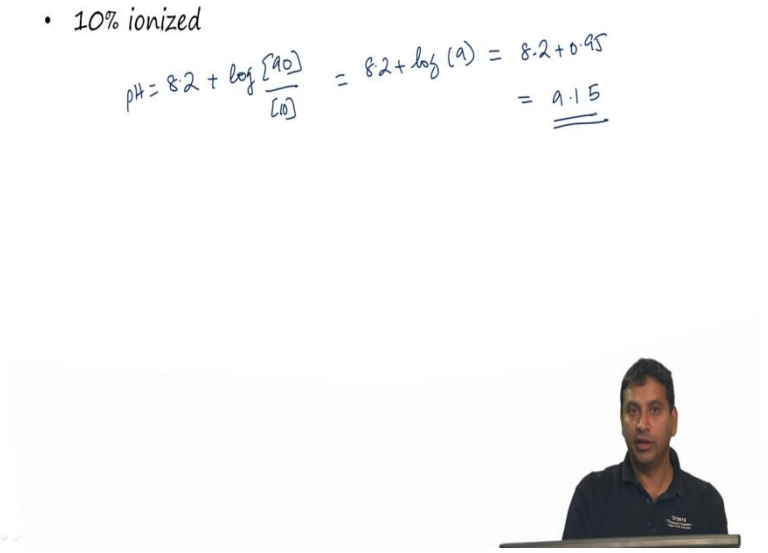

So in order to look at the 10 percent ionized case, the pH = 8.2 which is pKa of the molecule + log of 90 by 10 okay. So 10 percent ionized means it is going to be 90% of the unionized form or the unprotonated form and so this value is going to become 8.2 + log of 9 which is the value of 0.95 and that is going to give you 8.2 + 0.95 which is going to give you 9.15 okay, so again this pH is not practical in the system.

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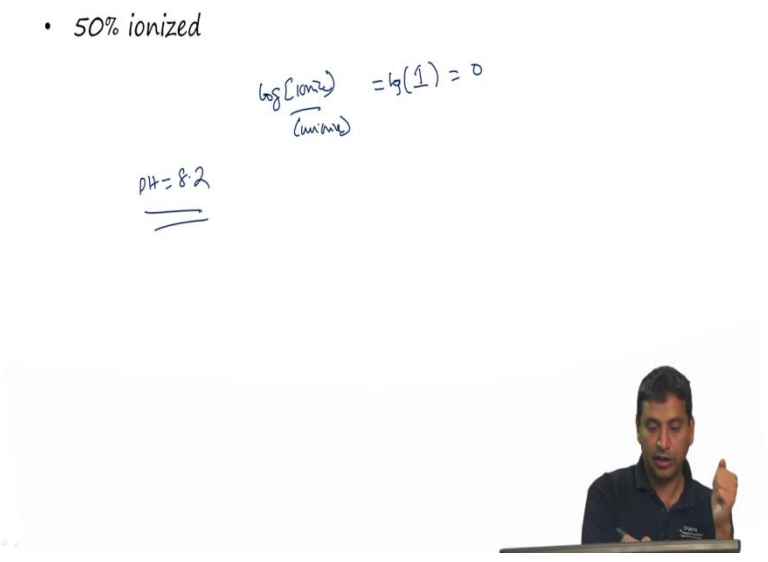

So in the case of 50 percent ionized so you have log of ionized by unionized equal to be this ratio is going to be 50 by 50 which is going to give you 1, log of 1 is 0 and so the pH would be 8.2 okay.

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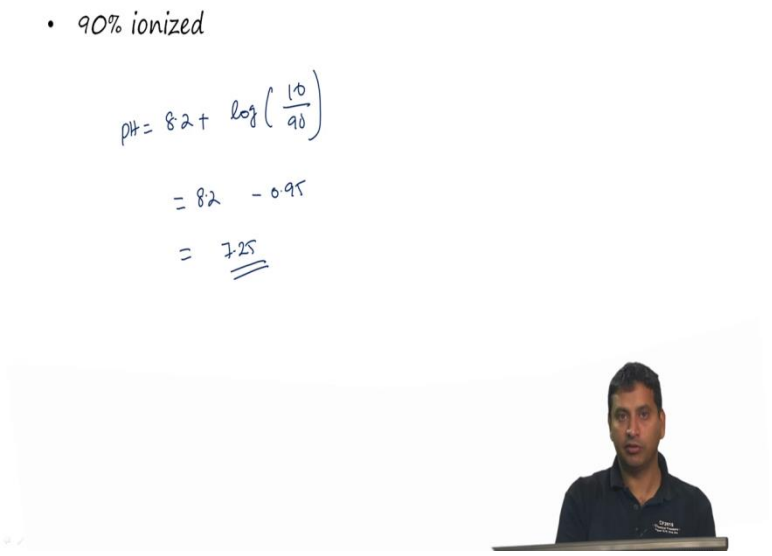

The next case, if you want it to be 90 percent ionized then pH = 8.2 + log of 10 divided by 90, so this number becomes 0.95 only thing this has a negative number, so 8.2 – 0.95 will give you 7.25, so the blood plasma level the pH is around 7.4 and so we would expect this to be 90 percent ionized in the blood plasma.

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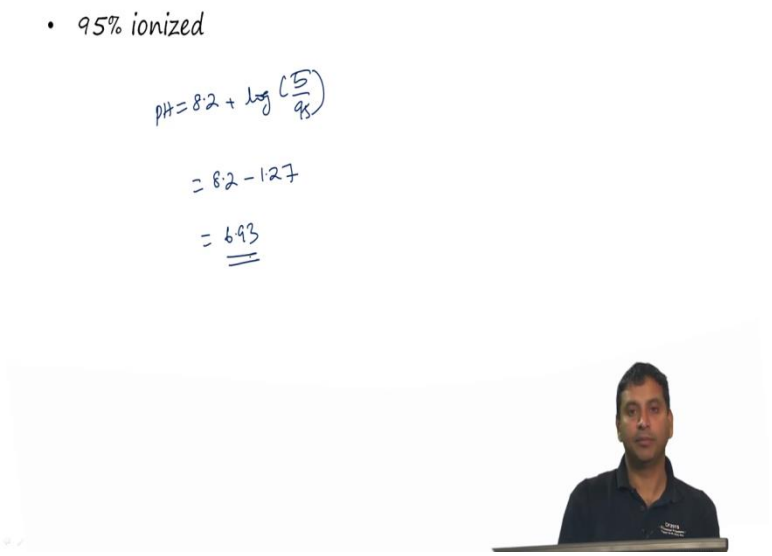

The last part is 95 percent ionized, so the principle is the same pH = 8.2 + log of 5 divided by 95 and so this would be 8.2 – 1.27, I suggest that you go back and do the calculation yourself and this will give us a value of 6.93