THE TOX LAB

Podcast Transcript

Episode 25: Mitragynine and 7-Hydroxymitragynine - Uncovering Kratom's Alkaloids

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TRANSCRIPT

Welcome back to the Tox Lab. I'm Rebecca. I'm Rob. This week we're looking at mitragynine and its related compounds found in the plant kratom. Rebecca, how do you pronounce this? I think I pronounce it kratom, but I'm not entirely sure. It's one of those words where I've learnt it by reading and I'm not actually sure what the correct pronunciation is.

I believe the American Kratom Association call it kratom, but actually I think there's some debate as to what's correct. Obviously kratom is the westernised word, but it's a plant from Southeast Asia and a few countries call it different things. So I'm not sure there is a right or wrong answer to this. Anyway, enough about linguistics.

Let's talk about some toxicology. Rebecca, what is kratom, mitragynine and things like that? So kratom is a tropical evergreen tree native to Southeast Asia, found in countries like Cambodia, Thailand and Indonesia. It's been utilised in herbal medicine for many years as it has opioid-like properties and some stimulant effects.

It's often chewed, smoked, drunk as a tea and taken in a capsule. Approximately 40 different alkaloids have been isolated from kratom and mitragynine is one of the most abundant alkaloids found, making up approximately 60% of the alkaloids in kratom. Its effects are concentration-dependent, so it can act as a stimulant at lower concentrations and then act as a sedative at higher concentrations. So mitragynine acts on opioid receptors as well as adrenergic and serotonergic receptors.

It's a partial agonist at the mu opioid receptor and a competitive antagonist at the kappa and delta opioid receptors. So mitragynine is metabolised by cytochrome P450 enzymes, mainly CYP3A4, to produce a 7-hydroxymitragynine metabolite. And this seems to be approximately 40 times more potent than mitragynine when assessing its opioid activity.

So mitragynine also has lots of negative effects, so people can present with nausea, diarrhoea, and potential seizure activity has also been reported, along with agitation, tachycardia, drowsiness, vomiting and confusion. Quite serious complications like AKI, hepatic injury, cardiotoxicity, acute respiratory distress syndrome, seizures and coma have also been reported. So kratom is quite interesting, isn't it? It's not something we see a lot of in the UK, but it is definitely present.

I've certainly come across one or two cases where we've detected its use. But in general, mitragynine is not a compound that we encounter all that often. I believe the market is quite different in the US. In the US, it is currently not banned and products containing kratom, mitragynine, and 7-hydroxymitragynine are sold fairly openly in places like smoke shops, petrol stations, or gas stations in the States.

And so I think the use of mitragynine products is quite a bit bigger there. I'm not sure what its use is like across Europe. I've got no real feel for that. No, I don't either.

So while mitragynine and kratom aren't controlled, the DEA have highlighted them as drugs of concern. So they're paying close attention to them. So it's not banned in the US, but it is on the DEA's radar. Yep.

So why don't we jump into some papers, Rebecca? First paper we're looking at is post-mortem distribution of mitragynine in a number of cases, correct? Yep. So the first paper we're going to discuss today looks at post-mortem distribution of mitragynine and 7-hydroxymitragynine in Texas.

So they were seeing a lot of mitragynine pop up in their post-mortem casework, but they had no real sense of its stability or whether it was susceptible to post-mortem redistribution and things like that. So they've taken 51 cases that they had between January 2023 and April 2024 and looked at mitragynine and 7-hydroxymitragynine across all the different sample types they had. They had cardiac blood, femoral blood, vitreous humour, urine, and they even had some tissue specimens as well. The age range for these cases was from 18 to 72 years old, with the mean age being 39, 82% of whom were male and 94% of whom were Caucasian.

So the first experiment they carried out was looking at the stability of mitragynine and 7-hydroxymitragynine in whole blood samples, because they had no real feel for how long you could detect it based on how long the sample had been stored for. So they spiked mitragynine and 7-hydroxymitragynine into whole blood, kept it in the fridge and then repeatedly tested it. And they found that mitragynine was stable for up to 30 days, but 7-hydroxymitragynine was only stable for up to seven days. This was a concern I had when I did have one of these cases where we detected mitragynine, because it took a while to get the 7-hydroxymitragynine reference material in.

And having read a lot about the instability of 7-hydroxymitragynine, I'm desperately trying to find some way of preserving my samples, trying to freeze them at minus 80 to preserve what was in there. So the next thing they looked at was the relationship between mitragynine and 7-hydroxymitragynine across the different sample types within each case. And they found that there was quite a large mitragynine to 7-hydroxymitragynine ratio, so more mitragynine than metabolite.

And they kind of hypothesised why this might have been. So death following acute exposure to a large amount of mitragynine might mean there's not enough time to produce much metabolite, and therefore that's why the ratio is off. Mitragynine has quite a long half-life relative to 7-hydroxy.

So again, that could be why the ratio is the way it is. Also, as we've just discussed, 7-hydroxymitragynine is unstable in biological samples. So it could just be that we're not seeing it. Or it could be down to post-mortem redistribution.

So to assess post-mortem redistribution, they looked at the concentration of mitragynine and 7-hydroxymitragynine in cardiac blood versus femoral blood, so a central site versus a peripheral site. So for mitragynine, the concentration ratio from cardiac blood to femoral blood was 1.37. And for 7-hydroxymitragynine it was 1.08. And there was a lot of variability between each of the cases which I think might be down to the delay between time of death and sample collection.

So it looks like in addition to being unstable, there's also some degree of post-mortem redistribution going on, and this effect is more pronounced in cases with a longer post-mortem interval. Yep. This is the sort of thing we do see with a lot of drugs, isn't it?

That during that interval between death and sample collection or analysis, the drug levels can change. They did have three cases where they had antemortem and post-mortem samples. In the post-mortem samples, the concentration of both mitragynine and 7-hydroxymitragynine was greater than in the antemortem samples. In two of these cases, the femoral and cardiac blood concentrations at post-mortem were about double what was seen in the antemortem samples.

And the time delay between death and the post-mortem was about 36 hours. Okay, so A, that's quite a big difference, isn't it? And B, 36 hours is a fairly short post-mortem interval. Yeah.

Compared to what we see. So, okay. I think these sorts of papers are important to highlight stability issues in drugs that we don't see very often, or how they're affected by the post-mortem interval. Because it does show with mitragynine that it is both unstable in samples that are collected and will change in the post-mortem interval.

So it is something that needs thinking about when interpreting cases where we are seeing mitragynine. And this is particularly complicated, isn't it? Because one process will make it go up and one will make it go down. And that does make things really tricky.

Yeah, I really like this paper. It's got a lot of data in it. There is a lot to digest, isn't there? And it does show just how variable concentrations of post-mortem mitragynine are across cases.

We don't obviously have a lot of the specific case information. There's no data in here about whether mitragynine was thought to be contributory or not. Even just showing that the post-mortem redistribution happens is really quite helpful. So why don't we move on to our second paper, Rebecca?

So this is an older paper, isn't it? This one caught my attention really because it was looking at the different effects of mitragynine and 7-hydroxymitragynine, the metabolite. So Rebecca, why don't you introduce us to this paper? So in this paper, they wanted to look at the respiratory depressant effects of mitragynine and 7-hydroxymitragynine.

So one of the things they did was give mice morphine, mitragynine and 7-hydroxymitragynine in increasing doses and measure respiratory depression using whole-body plethysmography, which is a bit of a mouthful to say. That is a mouthful. Can you explain what it means? Because I don't know what it means.

So it's a technique for assessing lung function. And I'm assuming in this case, because they're looking at mice, that they're putting mice in a sort of sealed container, and then they can measure the total amount of air in the lungs and the amount of air that's being exhaled and inhaled and things like that. So they're directly assessing respiratory depression.

Yeah. So morphine and 7-hydroxymitragynine showed a dose-dependent decrease in minute volume, which is the total volume of air moved into and out of the lungs per minute, between about three and 30 mg per kilogram, whereas mitragynine at three mg per kilo showed no significant changes to respiration. At 10 mg per kilo, there was significant prolonged respiratory depression, but when you started increasing the dose, you reached a ceiling effect. So all three did cause respiratory depression, and 7-hydroxymitragynine caused a bit more respiratory depression?

It was on par with morphine. On par with morphine. And as you increased the dose of morphine and 7-hydroxymitragynine, respiratory depression was more pronounced, but you didn't see that with mitragynine. No.

They hypothesise that the respiratory-depressant effect of mitragynine was down to the 7-hydroxy metabolite, and as you sort of increase the dose of mitragynine, you kind of reach a bottleneck where you can no longer produce more metabolite, and that's why as you start increasing the dose, you don't get any more respiratory depression. So within kratom preparations, there is both mitragynine and 7-hydroxymitragynine, but also mitragynine works as a bit of a prodrug and forms this more active metabolite in vivo.

You saturate your metabolism, and therefore there's sort of a limit to the amount of 7-hydroxymitragynine you can produce, and therefore to the respiratory depression. And they did also assess this by inhibiting the CYP3A enzyme, which is responsible for converting mitragynine to 7-hydroxymitragynine, with ketoconazole, and there was a significant decrease in mitragynine-induced respiratory depression after this, which again kind of shows that the respiratory-depressant effect of mitragynine is probably down to the metabolite.

And important to note, when they inhibited with ketoconazole, the respiratory-depressant effect of 7-hydroxymitragynine remained. So it does sound like this hypothesis may well have weight. So they also

looked at hot-plate latency, which is something we've talked about on this podcast before. And morphine, mitragynine and 7-hydroxymitragynine all had similar degrees of antinociception and duration of action.

Did that show the ceiling effect? They didn't see any significant differences between morphine, mitragynine and 7-hydroxymitragynine in this assay. That's interesting. But when they did the hot-plate latency after the pretreatment with ketoconazole, only 7-hydroxymitragynine induced a significant level of antinociception.

Okay, so it probably does confirm that 7-hydroxymitragynine is not only responsible for the respiratory depression, but also for the pain-blocking effect. So this is quite interesting, isn't it? So it does suggest that you've got an effect similar to, but not the same as, codeine being metabolised to its active metabolite morphine. It's kind of similar to what we're seeing here.

One of the things with codeine is that there's quite a lot of variation in metabolic phenotype. Now, that's mostly through CYP2D6. In this case, we're looking at CYP3A, but I think that's quite polymorphic too, isn't it? Yes, and they do discuss it in the paper that variability in this enzyme might increase risk with people taking mitragynine.

So if you've got an overactive enzyme and you're producing more 7-hydroxymitragynine, you're therefore more at risk of developing respiratory depression. And most people don't know their metaboliser phenotype. No, it'd be interesting if people did know. I'd quite like to know mine.

I'd quite like to know mine. But maybe that's just because we're a bit nerdy. So it does mean that two people taking the same dose could have different effects just based on their genetics. And we do know that with a lot of these cytochrome P450 enzymes, you can get drugs that induce enzyme activity.

So for example, some barbiturates and antibiotics can induce CYP3A, which again will increase the risk of respiratory depression in those sorts of cases. Or as we've seen, some can inhibit it completely. So the final paper we wanted to look at is not so much a formal research paper published in a journal, but actually an alert put out recently by the CFSRE, the Center for Forensic Science Research and Education in the US, looking at lab testing of some of the commercially available 7-hydroxymitragynine products that are now becoming available.

So in March 2025, they conducted a variety of different test purchases of powders and pills from smoke shops and tested them to see what was in them. So a lot of them contained 7-hydroxymitragynine as their primary compound, followed by mitragynine and mitragynine pseudoindoxyl, which is approximately a hundred times more potent than mitragynine. So another related compound that's even more potent than the 7-hydroxy. The reason that this report sort of resonated with me was that I had only just read the paper looking at the respiratory depression effects being mediated through CYP3A.

And so products are now being sold as containing 7-hydroxymitragynine as opposed to mitragynine. As we've just seen, this appears to be the compound responsible for the respiratory depression. So when I was saying earlier about how this is similar to codeine, with 7-hydroxy being like morphine, these products are like skipping the codeine and just selling the morphine, right? Yeah, and also because of this, these 7-hydroxymitragynine-containing products open up a greater risk of causing respiratory depression and therefore a greater risk of overdose and death associated with taking large quantities of these.

Yeah, it's really interesting, isn't it? So in general, although it's controversial, kratom doesn't seem to cause fatalities to the same degree as some pharmaceutical opioids. Whether it does or not, I think is up for debate, but it certainly appears to carry less risk. But as we're now moving towards products which are more refined forms of kratom, perhaps selectively extracting the 7-hydroxy or even possibly, and I don't think we really know actually, whether these are selectively extracting 7-hydroxy or whether it's taking mitragynine and chemically altering it.

Could these products suddenly contain a lot more risk, but possibly be marketed on the background of kratom seeming relatively safe? The other thing this report got me thinking about is whether we need to start thinking about looking for some of these other more potent but less abundant compounds. I mean, I definitely think it's something to think about. As we said earlier, mitragynine pseudoindoxyl is approximately a hundred times more potent than mitragynine itself. I think the other thing from this report also was the

sheer diversity of products that are being sold freely in the US as mitragynine-related products.

It talks about pills, but it also talks about gummies and beverages. And it also says ice cream cones, which I thought was slightly strange. That did intrigue me, but I'm sure I've seen on socials that you can get tiny little ice cream cones that contain THC and things that people snack on. So I'm assuming it's the sort of similar market they're trying to hit, but with mitragynine instead.

So miniature ice cream cones? Yeah, and they're like filled with chocolate or things inside, so it's just the cone. Okay, in my head it was like a 99 ice cream with that dry wafer cone and people were just eating the dry wafer cone. No, they're definitely filled with something.

That makes much more sense. It's interesting, isn't it? Obviously from a UK perspective, we don't see a lot of kratom or mitragynine, as I said earlier, but it does seem to be quite big in the US. And I do wonder where the market is going to lead.

I'm certainly aware that there have been a few cases in the UK. I think the other thing that really interests me about kratom is just how complicated it is. I remember analysing it when I did have a case and I had produced a beautiful method on our triple quad using the reference material. Chromatography looked great.

And then I ran my actual sample and so many of the other alkaloids in kratom are isomers of mitragynine. The real sample just looked like an absolute mess. You couldn't tell all of the isomers apart. Back to the drawing board.

So what does the future hold? That's a good question. I think it's definitely something to watch to see whether it reaches the same popularity on the UK market. Yeah, it'll be interesting to see.

I'd also like to see what happens in the US with regard to this move from pure kratom herbal products to refined products. Possibly, will we move even further down the potency route? Will we be seeing products containing the pseudoindoxyl as the primary component? It'll also be interesting to see whether the DEA do introduce any sort of controls with regard to mitragynine and its metabolites or whether it's just one they're aware of but don't see a need to schedule.

So I think they did try to introduce control some years ago and there was a huge public backlash. Oh, okay. Although, as we've seen, the market has subsequently changed. Perhaps controls on 7-hydroxy products might well be indicated.

So in summary, as toxicologists, this is getting complicated, right? Firstly, the analysis of mitragynine and 7-hydroxy is hard due to instability and post-mortem redistribution. We're now seeing massive market shifts towards more potent compounds and also compounds that maybe don't have such an inbuilt safety inherently due to the way that they're metabolised. Therefore, potentially, these compounds are going to become more relevant in the post-mortem sphere but also potentially in the clinical sphere as well.

I guess it really is a case of watch this space, isn't it, to see what happens with regard to the market and whether this sort of trend will continue towards higher-potency kratom products, and therefore what sort of response there will be. I've certainly learned something this week looking at the post-mortem redistribution. That really was quite interesting for me. Yeah, and that's definitely going to be something in the back of my mind if we ever have another mitragynine case, to help aid interpretation.

Okay, so I think we're going to wrap it up there. I hope you've enjoyed listening this week. Do like us, follow us, tell your friends. And if you've been with us for a while now, thank you for coming back and listening.

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we discussed today will be linked in the description of the episode as well, if you want to check them out.

Hope you all have an amazing week and we'll see you next time. Bye.