Episode 46: The Kappa Hypothesis - Medetomidine, Dysphoria, and Hallucinations

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Transcript

Hi everyone, welcome back to the Tox Lab. I'm Rebecca. I'm Rob. This week we're going to be taking another look at veterinary drugs emerging in street drugs. Some of the effects they've been having on people and possibly even solving the mystery as to what dogs dream about when they come out of surgery.

You're just going to have to trust me. Yeah, I do. Rebecca, what do you think dogs dream about when they come out from surgery? I don't know, probably like running around in treats.

Sausages, right? Yeah. The classic was they'd be chasing sausages or chasing balls. Well, that might be the case, but we're going to come back to this point a little bit later on.

Possibly there's a darker side and we're going to explore that a bit today. But that's not the primary focus of today's episode. The primary focus of today's episode is to take another look at medetomidine. We mentioned this a few weeks ago in an episode looking at emerging adulterants in the drug supply in the US.

And drugs like xylazine, medetomidine are featured quite heavily on this podcast, actually. They've been fairly regular occurrences. And really, there's two reasons. The first is that it is a big up and coming issue.

And secondly, I'm going to be honest, I'm just really interested in the pharmacology of some of these drugs. They're really, really interesting drugs. And a paper caught my attention this week, or our attention, you spotted it too, didn't you? Looking at some of the effects reported by people who use drugs which have been shown to contain medetomidine.

And in particular, hallucinations were reported, which surprised me. medetomidine is what we call an alpha-2 agonist and leads to sedation. We use alpha-2 agonists clinically, and hallucinations have never really been reported outside of a few adverse reactions. And so this caught my attention.

Is there something else going on? And we're going to be exploring that this week. Before we jump into today's episode, if you want to stay up to date with our content, you can find us on Instagram at @the_tox_lab. We also have a LinkedIn page, which we're fairly active on over there.

And for those of you who don't use social media, but still want to get in touch with episode suggestions or comments about our episodes, you can email us at thetoxlab@gmail.com. So Rebecca, why don't we just dive in first to the paper? So this paper was a retrospective analysis using data from a public drug checking service, and it was the UNC street drug analysis lab. And they looked at 11,363 samples that were analyzed by GCMS from the 7th of December, 2022 to the 11th of April, 2025.

medetomidine was identified in 278 of these samples, and in 136 of these was the most abundant drug present. Individuals sending these samples off were expecting samples to contain fentanyl, possibly xylazine, possibly heroin. And in the medetomidine positive samples, fentanyl and xylazine were also reported. Of the samples containing medetomidine, eight other substances on average were also found compared to three substances in all other sample types and co-occurring substances

included 4ANPP, procaine, lidocaine, BTNPS, caffeine, heroin, but these were also present in a lot of other samples.

So they did also interview individuals about the effects that these drugs were having on them, and hallucinations were reported in 18% of samples containing medetomidine, which was significantly more likely than samples containing other drugs. And they did allow individuals to free text and describe the sensations they were feeling, which I found quite interesting. So people described samples containing medetomidine as feeling trippy. One person said they were tired for days, it felt trippy like DMT, incoherent for hours, and there were several other peers who were all very scared.

Others described it as psychedelic, dissociative-seeming, lots of sweating, heavily sedating, so all quite negative effects overall. So a drug checking service in the US tested drugs, identified what was in them, asked the users how these drugs made them feel, and noticed an association between medetomidine being positive in the samples and hallucinations being reported. Of those hallucinations reported, most of them described a very negative effect. And I did do some digging on Reddit as well to see if there were any other user experiences published.

And people describe very dysphoric hallucinations, people feeling intimidated or scared, they describe visions at the corners of their eyes and things like that. So there does seem to be something in this. So let's talk a little bit about medetomidine itself. It's used clinically in healthcare as dexmedetomidine, one particular isomer.

It works as a sedating agent. As we said, it's what we call an alpha-2 agonist. And it's not used in the UK, interestingly, but it is used quite a lot in the US in intensive care units. And it's actually used as a sedative that's associated with low rates of post-operative delirium.

medetomidine is also used in veterinary medicine. And in that situation, it's actually comprised of the two isomers, so levomedetomidine and dexmedetomidine. The reason dexmedetomidine is used in humans is because when medetomidine was first investigated in the 80s, the levo isomer was considered to have low alpha-2 agonist potential. And therefore, it wasn't considered useful as a sedative, it just had extra side effects.

So clinically, we use the dex form. What's occurring in the drug supply is the veterinary form, the racemic form that's made up of both levomedetomidine and dexmedetomidine. So we've got this enigma, haven't we? We've got a drug that's reported to have low rates of post-operative delirium and actually shown not to have these hallucinogenic side effects.

And yet we've got a population of people who use drugs reporting these side effects. So what could be going on here? So the people who are experiencing hallucinations do tend to be people with addiction, who are using these drugs chronically over a very long period of time. Some of these individuals have other mental health disorders such as schizophrenia, which seems to make people more likely to experience hallucinations when on dexmedetomidine, but I'm not sure we know why.

Yeah, there has been a case report in the literature, hasn't there, that dexmedetomidine did induce hallucinations in an individual with schizophrenia. So this particular case involved a 75 year old female with a five year history of schizophrenia. She attended this hospital with pain and limited movement in her right knee and was diagnosed with a patellar fracture that was then scheduled for an open reduction and internal fixation. It's important to note she'd not experienced any episodes of mental illness the previous year and all her vitals were stable on admission.

In the morning before her surgery, she took her regular meds, sodium valproate and risperidone and was then given a spinal anaesthetic of ropivacaine. And once this was achieved, she was given dexmedetomidine for sedation at a loading dose of 0.3 micrograms per kilogram. And then that

switched to continuous administration at a dose of 0.5 micrograms per kilogram per hour. At the beginning of surgery, the patient's vitals were all normal.

So she had a BP of 122 over 62, heart rate of 60, but half an hour after the operation began, the patient became dysphoric, confused and was unable to communicate, and removed her IV fluids. Her BP and her heart rate continued to rise and after the dexmedetomidine infusion was increased, the patient became increasingly dysphoric. BP rose to 145 over 72 as well as a heart rate of 88 beats per minute. A confusion assessment was carried out and she was positive for delirium, and the dexmedetomidine was discontinued.

And I think the conclusion of this isolated case report was that this could have been some idiosyncratic reaction to dexmedetomidine, but it does bear some similarities to what some of the users are reporting following medetomidine use in their street drugs. So how does this tie into what we alluded to about what dogs dream about after surgery? Well, what is very interesting is it has been reported that dogs who undergo medetomidine sedation also display signs of dysphoria. I don't know how, how do dogs report dysphoria?

I've no idea. So increased vocalisation, increased agitation. And so it's possible therefore, that dogs were experiencing the same thing. It makes me really sad.

So medetomidine in street drugs is a thing. Hallucinations following medetomidine in street drugs appear to be a thing. Hallucinations following dexmedetomidine are generally not a thing, but could be a thing in vulnerable populations. And probably a population of people who use drugs would constitute a vulnerable population.

So it could just be that this is a feature of medetomidine, but I want to have a look at some of the pharmacology and propose a bit of a hypothesis. Because when you were describing those hallucinations, Rebecca, and when I started to read about what users reporting on Reddit, it didn't make me think of LSD hallucinations. No. Instead, it made me think of the hallucinations which described by people who use drugs like salvia.

And salvia is a Mexican plant. It's got a long history of shaman rituals, but crucially, the active component that causes the effects that users describe is what we call a kappa opioid agonist. And users report similar feelings to the medetomidine effects, the dysphoric nature, agitation, potentially shadow people at the corners of their vision. And so it got me thinking, is medetomidine somehow activating the kappa opioid system?

We talked in the past about xylazine, haven't we? Xylazine is another veterinary drug that's emerged in street drug supplies. It's also an alpha-2 agonist. And relatively recently, was shown to be a kappa opioid agonist as well.

So putting two and two together, I'm wondering if there is some kappa activity from medetomidine. So the kappa opioid pathway is relatively understudied compared to the mu opioid pathway. So most people, when they think of opioids, they think of the mu opioid receptor, and this leads to euphoria and reward pathways. Kappa receptors are really the opposite.

They lead to dysphoria, and it turns down dopamine release in reward circuits. And they form part of our stress response. When we're under threat as organisms, they stop you chasing pleasure and focus on survival. And they act really as a counterbalance to the mu opioid receptors.

But at high activation, they can cause hallucinations, as we described with the use of salvia. And these hallucinations have been described as dysphoric and very different from the hallucinations described in classical psychedelics like LSD. And they're also altered in disease states as well. And actually,

addiction and schizophrenia are two disease states that have shown alterations in both the transcription of the natural ligands for kappa receptors, but also the actual kappa receptors themselves.

There's been alterations in different parts of the brain, downregulation in some areas and upregulation in others. It's known, therefore, that chronic drug use can actually prime this pathway. Therefore, if medetomidine had some kappa activity, it's possible that it would be more significant in these populations. And the other possible difference we're seeing here between ICU patients who were given dexmedetomidine and people on the street taking racemic medetomidine is the presence of that levoisomer.

In humans, it was basically written off as not helpful. In dogs, it's possibly having an effect that we've not really thought about. And so I'm wondering if there is more kappa activity of that levoisomer. Yeah, possibly.

Now, medetomidine was tested back in the 80s to see whether it had any opioid properties. And there is a paper which tested racemic medetomidine and concluded that there was no opioid activity. But xylazine surprised us because xylazine was the same story. And the way they tested opioid activity back in the 80s was against a purified mix of different opioid receptors.

And because mu opioid receptor is found much more frequently, if a drug didn't have significant mu opioid activity, it may have fallen through the net. So it'd be really interesting to see if there is any kappa potential of particularly levomeditomidine in a more specific assay. As I say, this is all just a hypothesis. So if this hypothesis is right, and actually, to be honest, even if it's completely wrong, this point still stands.

It just shows how drug users on the street can, without really consenting or without any way knowing what they're doing, can become essentially guinea pigs for pharmacology, right? Yeah, it's quite scary. Not only do you not know what you're buying when you buy something on the street, but also it might do things that actually are completely unexpected, because there's some interaction that's just not understood. I think it does have a potential knock on effect as well, doesn't it?

In terms of the way that people who use drugs are perceived, particularly in the media, how many times have we heard of the new zombie drug? Yeah. At least three or four different drugs have been called the zombie drug. And now suddenly, we've got the hallucinogenic drug.

Is this going to further stigmatize drug users? Probably, yeah. Yeah, and that's a problem, right? We certainly don't want that.

I think this also highlights the importance of like readily available drug checking services, if individuals are using drugs that then do feel a bit weird and aren't quite what they expect, being able to get them tested to see what's in them so that we can then make these connections and work out what might be playing a role in different user experiences. And then that can feed back into harm reduction services as well. For sure. I think this paper is really strong actually, because not only did it test the substances, but it also asked the users what was going on and actually identified this pattern.

And this pattern was quite strong, right? Yeah. There was a 12 times more likelihood of hallucination when medetomidine was present. So it does suggest there is a role in medetomidine leading to hallucinations.

What is interesting, going back to my hypothesis, again, is that xylazine, which is also a kappa agonist, and unlike medetomidine has been shown to be a kappa agonist, didn't seem to cause the hallucinations. That's weird. So it's possible that my hypothesis is completely wrong. Or it's a potency

thing.

We know that medetomidine is very potent compared to xylazine at alpha-2 receptors. Is levomeditomidine more potent at kappa? Possibly. Another possible thought with regards to medetomidine and its kappa potential actually is medetomidine was tested back in the 80s, but I'm not sure if its metabolites were.

That is a good point, yeah. So there's always a possibility that a metabolite might have a different receptor profile. That's a very fair point. Or not.

Who knows? Who knows? So really, to summarize, medetomidine is very much a thing in street drugs in the US. This study has shown a really surprising finding of hallucinations.

I've proposed a pretty outlandish hypothesis. I'd love to know what other people out there think. If there's anybody out there who does receptor assays or is really good at predicting binding potentials on receptors, or anything like that, I would absolutely love to know your thoughts. If you think I'm completely wrong, please tell me.

So I do hope you've enjoyed listening this week. I hope I've not ruined your thoughts of what dogs dream about when they've just come out of the vets. I still like to believe they're thinking of sausages, not seeing shadow people. But who knows?

I want to thank you all for listening and if you've liked what you've heard, do please give us a follow, give us a like, share with your friends, particularly with regards to my caparagonist challenge. If you work with people who might be interested, do send this podcast their way. I'd love to get the reach wider to people that are doing this sort of work. Hope you all have an amazing week and we'll see you next time.

Bye.