Episode 61: Naloxone in the Age of Nitazenes and Ultra-Potent Synthetic Opioids

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Transcript

I'm Rebecca. I'm Rob. This week we're going to be taking a look at naloxone and we're going to be asking the question in the age of ultra potent opioids, we've talked a lot about those, is naloxone still effective? Before we dive in too hard about what naloxone is, how it works and things like that, I wanted to have a look at antidotes in general because I think growing up there's this perception in the media and on TV, if somebody gets poisoned, there's an antidote.

Yeah. And what does that antidote look like? How is this portrayed? Generally, it's like a magic vial of stuff that you inject into someone and it cures everything.

They miraculously recover and get better and I think that's the sort of media portrayal of antidotes. And in reality, as toxicologists, we know that actually most things don't have an antidote and if they do have an antidote, sometimes the side effects are worse than what they're antidotal to, very, very rarely is there an antidote to something where you can give it to somebody and they can miraculously recover.

Naloxone is one of the few truly iconic movie style antidotes that can in the right circumstances completely reverse somebody's sedation, somebody's loss of consciousness, their slowing of their breathing purely with an injection or a shot up the nose and they can come around remarkably fast. So we're going to be looking at Naloxone in more detail. 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 page on LinkedIn and we're really active on that.

And for those of you who don't use social media, but still want to get in touch with episode suggestions or comments about episodes, you can email us at the Tox Lab.gmail.com. On a little bit of exciting news, before we get into this episode, we are being hosted on the website, drugimpairment.com, showcasing a select number of episodes. So if you've found us through that, welcome, we hope you enjoy all the other content that we have to offer. And yeah, just a big shout out to being included on that.

Yeah, do go and check out drugimpairment.com. Fantastic training resource. So what is Naloxone? Naloxone is actually an opiate compound.

It's a semi-synthetic opiate derived from the bane poppies in the same way that many drugs are. Unlike drugs like morphine and codeine and dihydrocodine and oxycodone and other things that are derived from these poppies, Naloxone actually has the opposite effect. It antagonizes the effect of opioids on the mu opioid receptor in the brain. And we'll dive a bit into the pharmacology about Naloxone once we've looked at some papers.

But the history is actually quite interesting. It was synthesized in the 1960s, originally a research tool. And at this point, we knew that drugs like morphine worked, but we weren't really sure how. And it was here that Naloxone was discovered that with a small chemical change, you could turn these opiate compounds into ones that didn't activate the receptor, but rather actually blocked the receptor.

And it was used to prove that opioid effects were receptor mediated. That was part of the journey for how we understood these mu opioid receptors. And it then directly contributed to understanding of the different subtypes of opioid receptor and also how we then understood concepts like affinity and potency and dose-dependent relationships of opioids. So it really was a critical research tool in understanding opioid pharmacology.

But it was much later, maybe in the 70s, that it was identified that this compound could not only be used as a research tool, but actually a useful antidote. And it became adopted in emergency medicine. Originally, within anaesthetics, they could reverse opioid analgesia. But later, as a first aid tool for treating street overdoses.

But we wanted to look at this idea of Naloxone-resistant opioids. Because this is a term you sometimes see in the media. They talk about ultra-potent opioids, and they talk about how they're not responsive to Naloxone. And we wanted to look to see whether there was any truth to that and what the pharmacology was behind this resistance.

And so our first paper actually looks at a series of hospitalizations due to ultra-potent opioids. We've talked a lot about ultra-potent opioids on this podcast. Compounds like fentanyl analogues, nitazenes. And these are compounds that work in the same way as drugs like morphine codeine, except they're very, very potent.

They can produce very significant clinical effects at very low doses. So Rebecca, why don't you introduce us to our first paper this week? So this first paper is a description of the Australian experience of nittacine poisoning as detected through local toxicosurveillance systems with particular focus on naloxone treatment. So this is a prospective series of patients with analytically confirmed nittacine poisoning that were identified by the Emerging Drugs Network of Australia and the Emerging Drugs Network of Australia Victoria.

These are both multicenter studies of illicit drug-related presentations to emergency departments across Australia and Victoria. So both these databases were searched for nittacine presentations between the 1st of July 2020 and the 29th of February 2024. 30 nittacine-related presentations over that period were found and this represented less than 1% of the total presentations to these databases. 72% of the individuals were male with a median age of 31 years.

5 had intentionally ingested an nitazene. 38% of individuals had believed they were taking an alternative opioid. And quite shockingly, 47% of individuals were unaware they were using an opioid at all. Presentations were all consistent with an opioid toxidrome with the median respiratory rate being 8 breaths per minute and a median GCS of 3 with a range of 3 to 8.

Myosis or constricted and pinpoint pupils were documented in 14 out of the 26 cases. And these are classic signs of opioid toxicity, aren't they? The pinprick pupils, the slowdown or complete absence sometimes of breathing. And actually that reduction in breathing, that's ultimately what can kill you.

That's the mechanism by which opioids can lead to significant hypoxia and ultimately death. Naloxone was administered in 23 of the patients and in 14 of these, this was provided pre-hospital through various routes. 15 patients received naloxone in the emergency department via an IV with a median total dose in the first hour post-hospital presentation of 400 micrograms and 4 patients subsequently received naloxone infusion. 10 patients in total were intubated with 5 needing to be intubated before they arrived at the hospital.

50% of the patients who were intubated received naloxone prior to admission. 13 individuals were admitted to the ICU with the respite managed in the emergency department. The median length of stay at the hospital was 17 hours and there were no deaths reported. Analytical testing confirmed the

presence of nitazenes in all samples with prothonitosine being detected in 23 cases and methanitosine being detected in 9 cases.

Other nitazenes that were detected included M. pyrrolidino ethanitosine in 2 cases, isthanitosine in 1 and butanitosine in 1 and ethadethanitosine in 1. And in 5 cases, 2 nitazenes were detected. They were able to quantitate the nitazenes in these cases, so 10 cases where prothonitosine was detected, the concentration on average was 2 micrograms per litre. In 5 of the methanitosine cases, they were able to quantitate and that had a median concentration of 3.6 micrograms per litre.

The lowest concentration associated with opioid toxicity in a patient that received naloxone was 0.7 micrograms litre for prothonitosine and 1.1 micrograms per litre for methanitosine. In 97% of the cases, multiple substances were co-detected and the most common co-detection was methamphetanin in 18 cases. xylazine was also detected in 4 and benzodiazepines both pharmacy school and novel benzodiazepines were also commonly co-detected substances. And actually, this is some interesting data, isn't it?

Because it's not often we get nitazene concentrations in anti-mortem cases, particularly with the numbers that we've seen in this case series. Very low concentrations, microgram concentrations as we would probably expect. Interestingly, the methanitosine concentrations slightly higher than the protonitosine, consistent with methanitosine being slightly less potent than protonitosine. So it fits quite nicely.

What I think is perhaps crucial here is that we're looking at the concentration on arrival at hospital or close to arrival to hospital. We don't know what kind of time frame there was prior to hospital and we think these compounds are cleared relatively fast. They're relatively short acting. So I don't know how much we can really interpret those concentrations too hard.

What I thought was quite interesting is the substances that co-detected alongside. But in Australia, there have been multiple public health warnings of nitazenes being detected in methamphetanin, in cocaine, in counterfeit benzos and in ketamine. Looking at the dose of IV naloxone that was given, this was comparable to those that have been used in other Australian case reports where heroin was the dominant opioid found. It is important to note this was IV naloxone, which is a higher bioavailability than intranasinal naloxone.

And in an American study using intranasinal naloxone, the mean cumulative dose was 4,400 micrograms, which might reflect the differences in bioavailability between intranasinal naloxone and IV naloxone. Yeah, I didn't mention that at the start. So in terms of what naloxone is available to first responders, there's two forms, one of which is intranasal. So it's really easy for people to use.

And often, this can be handed out to people who use drugs as first-line antidote treatment. The other option is either intramuscular or intravenous even naloxone, which, as you say, goes straight into the bloodstream and avoids some of the first-pass metabolism and things like that. The number of patients who received IV naloxone infusions in this study is also similar to the reported proportion of patients who have been exposed to other short-acting opioid overdoses, including heroin, fentanyl, and oxycodone in Australia.

So it's not like with the nittyzines, we're seeing more people requiring IV naloxone compared to other opioids that people are being exposed to. So what's the take-home from this study then? In this fairly large number of nittyzine exposures, the proportion of patients requiring IV naloxone was similar to other opioids. And so there doesn't seem to be any particular additional naloxone requirement.

Can we conclude that? You would think if they were, if you needed a high dose and more naloxone, more people would end up on a naloxone infusion. Okay. So naloxone infusion is generally considered

the sort of most extreme form of naloxone treatment.

A lot of these other patients have been given one or two doses pre-hospital. The relative number of patients on an infusion was similar to other opioids. So the suggestion from this paper is then that actually naloxone is as effective against nittyzines as it is against more traditional opioids, heroin, and so on. So let's explore a little bit then about what actually happens pharmacologically with naloxone.

So as I said at the start, it's derived from the Thebanes poppy, but it's chemically modified to rather than activate the opioid receptor, not activate the opioid receptor. It still binds to the opioid receptor. It's still got fairly high affinity for the opioid receptor, but unlike drugs like nittyzines, once it's bound to the receptor, it doesn't then activate it. And when you give naloxone to somebody that's got an opioid on board like nittyzines, it competes with the nittyzine to sit in that binding packet.

And if naloxone binds to a receptor, it's going to displace the opioid and stop the signal that the nittyzine is causing. And so this is the rationale. It acts as a competitive antagonist at the Mu opioid receptor. And crucially, it doesn't really do things to people that don't have any opioids on board.

We do have endogenous opioids of which our endorphins form part of that endogenous opioid system. And actually, in studies where they have given naloxone to people who don't have opioids on board, there are sometimes really minor effects such as increased pain susceptibility, just short-term while the naloxone works. So it's not completely benign, but clinically it's considered to be completely benign. It doesn't have any significant effects on people who don't have opioids on board.

So are there any limitations to naloxone? So crucially, it does need to be given in a very timely manner, doesn't it? If people take a massive opioid overdose and completely stop breathing, really they've got minutes to get oxygen supplied back to the brain. So naloxone does need to be given very, very quickly.

It won't reverse things that aren't opioids, so it won't work if there is xylazine on board or if there are benzodiazepines acting or alcohol or other things like that. But all in all, it is actually a very powerful first aid tool. So this Australian data generally suggested that naloxone probably is effective based on the proportion of patients having received infusions. Nitazenes in general are fairly potent compared to morphine.

The most potent nitazenes are about a thousand times more potent than morphine, such as etonitazene and N-pyrrolidino etonitazene. But actually, I got thinking, is there something more potent out there? And if there was a more potent opioid, would that be naloxone resistant?

And we found this case report. It's not a new case report. It's actually a fair few years old now. And Rebecca, why don't you just dive in and then we'll unpack it.

So carfentanil is an extremely potent opioid. It's approximately 10,000 times more potent than morphine and 100 times that of fentanyl. It's approved for use by vets as a tranquilising agent in wildlife management environments and in zoos to rapidly incapacitate large hoof stocks such as moose, elk, bison and other exotic wildlife so that they can be examined and to allow for procedures to be performed. So going back slightly to movie references at the start and iconic antidotes.

This is that iconic scene from all sorts of films where they shoot an elephant with a dart and the elephant collapses. That is often carfentanil. So a 42-year-old male vet was shooting darts containing 1.5 milligrams of carfentanil and 50 milligrams of psiloxane to sedate an elk for TB testing. He managed to shoot a dart at a tree and whilst dislodging this from the trunk, he accidentally splashed himself with the contents of the darts in his face, eyes and mouth.

He immediately washed his face with water but within two minutes he became drowsy and was then administered 100 milligrams of naltrexone from the antidote kit by his co-workers. He was then transported to the emergency department one hour later and appeared well with only mild and transient chest discomfort. He presented with a blood pressure of 134 over 88, a pulse of 75 beats per minute, a respiratory rate of 18 breaths per minute and had an OT sat of 98% on rim air.

On physical exam his face appeared flushed but his pupils were normal in size and reactive to light and all other exams were normal and he was observed for 24 hours but remained asymptomatic and was then discharged. Whilst this is a single case report, if you wanted any evidence that ultra potent opioids can be reversed with reversal agents, this case demonstrates it really well, doesn't it? And it's actually quite common for vets using carfentenil darts to carry the antidote for this reason. In this case they use naltrexone, didn't they?

Yep. Which I'm just going to unpack slightly. That is a different antagonist opioid. It's similar to naloxone.

It's got different kinetics. It's got a much longer half-life but in principle pharmacologically it does exactly the same thing. It displaces opioids at the receptor and stops them being activated. So, so far evidence is saying actually naloxone resistance with these ultra potent opioids.

That doesn't seem to be a thing, right? We've actually now got some pharmacological data that looks a bit deeper into this to see whether at the receptor level there's actually any differences going on between ultra potent opioids and more traditional opioids. So, as we've discussed, there are some theories that standard naloxone doses may not be as effective for these very potent synthetic opioids. And there are two major mechanisms that are kind of postulated surrounding the limitations of standard naloxone antidote-dosing.

So, one is the renarcotization theory which is basically a pharmacokinetic mismatch between naloxone and the synthetic opioids causing a single naloxone dose to be insufficient for sustained overdose reversal. So, a potential mechanism for this is that naloxone is relatively hydrophilic compared to synthetic opioids and is rapidly metabolized to naloxone-3-glucuronide, which can't get into the brain, but synthetic opioids are more hydrophobic and are absorbed passively by adipose tissue so that when naloxone is metabolized the synthetic opioids are able to agonize the mu opioid receptor again.

So, even though you've had that initial displacement when naloxone is metabolized that synthetic opioid can come back in and bind to the receptor and elicit an effect. And I think that differences in half-life when it comes to opioids being reversed by naloxone is well recognized. We know, for example, drugs like methadone have got a very long half-life and it's commonly seen that you can reverse a methadone overdose with naloxone but you need to give people multiple doses or put them on a continuous infusion because the half-life of methadone is so much longer than the half-life of naloxone.

And the other theory is naloxone resistance and this is a theorized phenomenon where naloxone has a limited ability to reverse synthetic opioid agonist poisoning. The aim of this paper was to determine EC50s for fentanyl, carfentanyl and acrylfentanyl, and an IC50 for them after competition with naloxone which was also generated to assess the reversibility of the receptor-ligand interaction. So, an EC50 is the effective concentration 50, or the concentration of a drug that will activate 50% of its maximum effect.

So, if you've got a cell-based assay looking at receptor binding and receptor activation it's the concentration that will cause 50% of that activation. An IC50 is the inhibitory concentration of 50%, so the concentration of naloxone required to displace half an opioid's effect at its receptor. So, after

determining EC50s, acrylfentanyl had a potency approximately 50% of fentanyl and carfentanyl's potency was nearly 100 times that of fentanyl. They then stimulated the cells with a concentration equivalent to an EC90 for each compound and a different dose of naloxone was then given to generate a dose-response curve.

This allowed them to determine the concentration of naloxone that was required to reverse an EC90 dose of a synthetic opioid and this then allowed IC50 values to be calculated for naloxone against the synthetic opioids. So, let's just break down what they did. So, they've taken these cell models these receptor models they've incubated them with a concentration of the drug that activates 90% of those receptors and these are S-shaped curves so they almost never reach 100% saturation. 90% is as close as you get without going to really, really silly doses.

They then used naloxone and essentially titrated that to work out what concentration would lead to 50% inhibition. So, importantly in this study naloxone did reverse the agonist activities of both acrylfentanyl and carfentanil. Interestingly, acrylfentanyl required double the naloxone dose of fentanyl to reverse the agonist activity despite it being half as potent as fentanyl. Carfentanil, unsurprisingly, required a significantly greater concentration of naloxone in order to antagonise a challenge of its EC90.

So, while this paper is based on ultra-potent fentanyl analogues, people have done this with nitazenes and they do show very similar results in that more naloxone is needed to cause inhibition. So, let's break it down a little bit then. So, there is this pharmacological phenomenon. We know that if we study these ultra-potent opioids in cell models, naloxone reversal does work.

It does work but there are some dose differences with how much naloxone you need. Let's compare this to the clinical data. The clinical data suggests that naloxone does work and possibly doesn't actually require much more, if any more, naloxone than would typically be used. We do kind of need to put some of this into context, don't we?

Because on the one hand, nitazenes and fentanyls are way more potent than more traditional drugs like morphine. On the other hand, people are using much lower doses. So, although there is a difference in potency, there is also a difference in the amount of the drug that's on board. So, it could well be there is this mismatch between pharmacological theory and what's actually happening in test tubes versus what's happening clinically.

I do want to touch on the real world implications of naloxone and where some of this naloxone resistance could be coming from. I mean, firstly, clearly, massive overdoses of ultra-potent opioids are possibly more likely in the sense that it takes much smaller dosing errors to lead to very large overdoses. So, it is certainly possible that you're going to come across very, very high relative concentrations when you account for potency of some of these newer opioids purely because it's easier to make a dosing error for a dose to be wrong and for a dose to be more toxic.

We also need to consider some of the other things that are going on in the drug supply. We've talked a lot about xylazine and medetomidine and these are drugs that are now emerging within illicit drug supplies and crucially, they won't be antagonized by naloxone. So, you could well have somebody that is under the effect of opioids and so has the classic pinprick pupils, but also a degree of their sedation is caused by something like xylazine. So, it is possible for this clinical phenomena to happen even if the nitazene or the fentanyl itself is still sensitive to being displaced by naloxone.

I do think that finding about how a less potent fentanyl analog still required more naloxone was quite interesting and that does seem to suggest there are differences between different classes of opioids that perhaps we don't quite understand. So, what's the take-home message from all of this then?

Clinically, naloxone is still effective against highly potent novel opioids and the argument that it doesn't work really probably isn't based on anything. That said, at the receptor level, there could be some interesting things going on and there may well be some interactions that need to be considered.

So, I guess in summary, naloxone potentially is that antidote that many people imagine a toxicological antidote to look like. Unlike most antidotes, this really is one that can bring people up off the ground in a matter of moments. But it isn't magical either and it does have some limitations. It does still seem to work against ultra-potent opioids and in this age of ultra-potent opioids, naloxone is still a key first aid tool.

But, possibly, there might be some pharmacological truth to needing higher doses. Well, I hope you've enjoyed listening to us this week. Do give us a like, give us a follow, share with other people who you think might be interested. Hope you all have an amazing week and we'll see you next time.

Bye!