THE TOX LAB

Podcast Transcript

Episode 30: Methamphetamine Enantiomers Explained - Mirror Image Molecules in Drug Testing

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TRANSCRIPT

Welcome back to the Tox Lab. I'm Rebecca. I'm Rob. This week we're looking at methamphetamine. Most people, when they think of methamphetamine, they think of Walter White, Breaking Bad, cooking up methamphetamine in the desert.

But actually it turns out methamphetamine's a lot more complicated than that. Before we jump into today's episode, if you want to keep up to date with our latest episodes, or want to get in touch to give us future episode suggestions or any feedback for any of our episodes, you can find us on Instagram at @the_tox_lab. We also have a page on LinkedIn, and for those of you who don't use social media but still want to get in touch, you can email us at thetoxlab@gmail.com. Imagine you test positive for methamphetamine, but all you've done is hit an over-the-counter nasal decongestant inhaler fairly hard.

That's actually the reality of methamphetamine, and we're going to be looking into that today. Methamphetamine actually exists in two different versions. Now these are called enantiomers. So you get what's known as D-methamphetamine, and you get L-methamphetamine.

D-methamphetamine is the version that Walter White cooks up. The other is found in nasal decongestants. So how can two versions of the molecule have very different effects? D and L-methamphetamine have both got the same molecular formula.

They've both got a virtually identical chemical structure except they're mirror images of one another. So if you imagine looking at both your hands, you've got a left hand and a right hand, and it's not possible to superimpose the two on top of one another. So they're different, but they're essentially the same. And because the way drugs work in the brain, they rely quite often on receptor binding.

The two different forms of methamphetamine have got different receptor binding profiles. So this leads to vastly different effects. D-methamphetamine causing the effects that we associate with methamphetamine use and L-methamphetamine doing very little other than clearing your sinuses. So D-methamphetamine has a greater overall potency for monoamine release and is more selective for releasing dopamine.

Whereas L-methamphetamine is primarily a selective release of the noradrenaline. So that's why you get the different effects between the two. One of the effects of L-methamphetamine is it causes vasoconstriction and this can therefore reduce nasal mucosal swelling and clear your sinuses. So with that in mind, Rebecca, why don't you lead us on to our first paper we're going to look at today?

So the first paper is looking at the Department of Health and Human Services' mandatory guidelines for federal workplace drug testing programs. Enantiomer testing can be used to determine whether methamphetamine is from an over-the-counter inhaler, in which case it'd be L-methamphetamine, or if illicit methamphetamine is present. They have quite a generous cutoff. So if D-methamphetamine is present at

greater than 20%, this is suggestive of an illicit source.

And I just want to jump in briefly here at this point. Vicks inhalers containing methamphetamine aren't available in all markets in the world. So this isn't something we see in the UK. In the UK, all forms of methamphetamine are controlled under the Misuse of Drugs Act.

So this is specifically an America thing and other places that sell Vicks inhalers containing L-methamphetamine. But also there shouldn't be any D-methamphetamine in an inhaler, should there? So this 20% cutoff is actually very, very generous. Twenty-four of the 37 Health and Human Services labs that this paper looked at were certified to do enantiomer meth testing.

They all used GC-MS with a chiral derivatizing agent. So 23 of these labs used L-TPC and one lab used MTPA. So let me just stop you right there for a minute. When you're doing testing for methamphetamine, most of the time you are testing for both D and L forms combined.

These labs are doing specific testing that can tell the L form and the D form apart. And they're using chemical derivatization. So they are converting the methamphetamine with a chiral-derivatizing agent in order to separate the L and the D forms. But actually most testing will only detect the presence of total methamphetamine.

So this paper kind of looked at three different things. It looked at the methamphetamine in over-the-counter inhalers. It looked at commercial standards that are either L-methamphetamine or D-methamphetamine. And then it evaluated proficiency testing.

So basically they sent around 18 different samples to all these different labs. And they knew what they'd put in there. And it was basically to see whether the labs could accurately determine whether it was L or D-methamphetamine and what sort of proportions there were. So they looked at six different inhalers that were all reported to contain 50 milligrams of methamphetamine.

Across the different labs, the concentration of these inhalers ranged from 65 to 81 milligrams. So a little bit higher than what they were stated to be. The lab that was using L-TPC as its derivatizing agent found D-methamphetamine to be present between 2 and 2.5% of the total methamphetamine across all six inhalers. Whereas the lab that was using MTPA didn't identify any D-methamphetamine.

And this was a trend that was kind of mirrored when they looked at the commercial standards. So the ones that should either be fully D-methamphetamine or fully L-methamphetamine. The labs that were using L-TPC found the D-methamphetamine to contain between 95.5 and 97.7% D-methamphetamine. And in the L-methamphetamine solution, it contained between 2.3 and 3.5% D-methamphetamine.

Whereas the one lab that was using MTPA identified the solutions as 100% pure. So some methodological differences in results. So with the proficiency testing, they wanted to look at the cross-reactivity of an immunoassay that was targeted to D-methamphetamine and to see whether L-methamphetamine would cross-react and cause a positive result and therefore reflex testing. And then they also wanted to determine the lowest concentration and the lowest percentage of D-methamphetamine that could be accurately quantified in a sample.

But it turns out that at high concentrations, L-methamphetamine was cross-reacting with the immunoassay screen that was targeted at D-methamphetamine. So leading to sort of a false positive that would then need downstream confirmation. And across all the labs that were using L-TPC, D-methamphetamine was reported at a percentage one to 3% higher than it should have been across all the different samples. And it's thought to be attributed to the fact that L-TPC is impure and does contain about 1% D-TPC, which is leading to the overestimation of the amount of D-methamphetamine that's present in the sample.

So MTPA seems to be a better chiral derivatizing reagent choice because it was able to correctly identify a hundred percent pure solutions. But this compound does damage GC columns and requires a lot more injector port and detector maintenance. So that's probably why only one of the 24 labs is using it. So over the counter, L-methamphetamine is a thing.

Illicit D-methamphetamine is a thing. The screening test was not specific for one or the other, so you could get false positives. But in general, all labs that were doing this enantiomer testing could reasonably well identify the difference between L and D with some slight overestimation in some labs based on the method. Yes, and I think that's why the cutoff is set so high because you do get this slight cross-reactivity that you can't really have it any lower than 20% because then you risk saying someone's used illicit methamphetamine when they haven't.

And they are quite polar opposites in terms of extreme, aren't they? One being highly illegal, highly psychoactive, the other being freely available over the counter to clear your nose. You don't wanna get it wrong. So the next paper we want to look at today also possibly has more relevance in the US than it does in some parts of the world.

And this was a study looking at the effects of the different enantiomers of methamphetamine on fentanyl-induced respiratory depression. So this paper looked at the enantiomeric contributions of methamphetamine on respiratory depression when combined with fentanyl in mice. So there's what is described as the fourth phase of the overdose epidemic in the US. Fentanyl's often being combined with stimulants and between 2013 and 2019, deaths involving stimulants increased by 317%.

And the overdose due to stimulant and opioid co-use showed the largest relative increase compared to either being used alone. So at low doses, methamphetamine's been shown to have a mild yet significant depressing effect on uncompromised basal respiration. And when combined with fentanyl, low dose methamphetamine exacerbates the opioid-induced respiratory depression. But interestingly, our high dose of methamphetamine actually reverses respiratory depression.

So I wanted to see whether the D or the L enantiomer contributed differently to this effect. And this is counterintuitive actually, isn't it? Because stimulants, you assume, will increase respiration, therefore have the sort of high dose effect. But this concept of a low dose methamphetamine actually causing respiratory depressant effects was a little bit of a surprise to me.

Essentially to do this, they gave mice D-methamphetamine and L-methamphetamine at different doses with and without the use of fentanyl and measured respiration rate, tidal volume and minute volume. And they didn't make them listen to The Prodigy in this experiment? No, they didn't. So first off, looking at D-methamphetamine, when that was given with mice pretreated with fentanyl, you get a significant dose-dependent increase in minute volume.

So at low doses, which they looked at as one milligram per kilogram, you get a pro-depressant effect. And then at high doses, which was 10 milligrams per kilogram, you get a stimulatory effect. You also get the same dose-dependent increase in respiration rate, in addition to minute volume, in both mice not treated with fentanyl and in mice that were pretreated with fentanyl. When looking at L-meth, you get a significantly decreased minute volume at low doses, so one milligram per kilogram and three milligrams per kilogram.

At 10 milligrams per kilogram, you don't get any alteration in this, but you do get some stimulation effects at 30 milligrams per kilo in mice that weren't given fentanyl. So even L-meth has some effect on respiration rate and it drives it in a dose-dependent way. Yes, but when these mice were treated with fentanyl and given L-methamphetamine, you just got a respiratory-depressant effect and they seem to be most potent at the dose of three milligrams per kilo. So L-methamphetamine actually made fentanyl-induced respiratory depression worse.

Yes. And you might be sat there thinking, hold on a minute, fentanyl, methamphetamine, mice. How is this relevant? But as Rebecca said at the start, in the US in particular, there is a lot of fentanyl use and a lot of methamphetamine co-use.

And so this could potentially be clinically relevant. If methamphetamine is D-methamphetamine, which is what it is assumed to be most of the time, I think, in these cases, then it may be having a pro-respiratory effect. But actually, if it's L-methamphetamine, it could be exacerbating respiratory depression. So why don't we move on to our third paper?

And this was the paper that caught my eye on LinkedIn and inspired this entire episode. So this next paper looks at enantiomer profiling of amphetamines seized in drug samples and in the blood of impaired drivers in Iceland. So between 2017 and 2020, the use of amphetamine and methamphetamine has been increasing in Reykjavik in Iceland. And this is based on samples of wastewater and they seem to have been seeing an increase in amphetamine and methamphetamine.

So this paper does look at both amphetamine and methamphetamine, but we're just going to focus on the methamphetamine findings for today. But I will link the paper in the description below if you want to go check out the other conclusions of this paper. Amphetamine, like methamphetamine, exists as two enantiomers. Instead of using GC-MS to determine the different enantiomers, in this paper they were using chiral UPLC tandem mass spec.

Twenty-six methamphetamine samples were seized, including 15 powders and 11 crystals. And 14 of these seized samples were D-methamphetamine and 11 of them were L-methamphetamine. And these were all seized as illicit drugs and actually a decent chunk of them, in fact, were not D-methamphetamine at all.

So looking at the blood samples taken in those who were driving under the influence of drugs, 236 samples were positive for methamphetamine with a median blood concentration of 185 nanograms per millilitre. Ninety-three of these were primarily D-methamphetamine with a concentration of 208 nanograms per millilitre. And 43 of these were L-methamphetamine with an average concentration of 155 nanograms per millilitre. And 100 of these samples were a mix with an average concentration of 190 nanograms per millilitre.

But this was quite surprising, wasn't it? It's generally assumed that illicit methamphetamine is the D version on the grounds that that's the psychoactive one. That's the one that people probably would seek. And yet this Icelandic data actually seems to contradict that, doesn't it?

Quite a lot of what was seized and what's been seen in driving under the influence samples is in fact the L fraction. And unlike in the U.S., L-methamphetamine isn't available over the counter in decongestants and things like that in Iceland. So this really is quite surprising. So to summarize all three papers, in the U.S., L-methamphetamine is a thing and is available over the counter as a decongestant.

And therefore it's routine for labs to tell the difference between D and L. There's quite clear clinical differences between D and L-methamphetamine as shown by the second paper. And particularly in cases of opioid-induced respiratory depression, this could be quite significant. And finally, the Icelandic paper actually shows that the assumption that all illicit methamphetamine is D-methamphetamine is possibly incorrect.

And so where does this leave us? I mean, it's a really tricky question. Part of me thinks maybe we should be considering looking to test for the D and the L because of their differences for respiratory effects and how that might influence our interpretation of a lot of casework, but it is quite tricky to achieve, as we've seen with the testing paper, that you do get variability with certain methodologies. Yeah, certainly where my head's at.

So for context, I'm sure there are labs in the UK that can tell the difference between D-methamphetamine and L-methamphetamine. But generally, this isn't something we often do or think about. And I'm wondering if maybe we've been sticking our fingers in our ears and pretending it's not a problem when actually it potentially could be. It's certainly making me wonder if we should be doing more to differentiate these enantiomers.

So in terms of the testing and how it's done, we sort of touched on it briefly, haven't we? But there is both chemical derivatization, which is what they were doing in that first paper. Or as the Icelandic paper showed, you can use chiral HPLC columns, so specific chromatography columns that can separate out these isomers. So it can be done.

It's just a case of developing the methods, validating the methods, bringing them into use. If it's not the case that all illicit methamphetamine is D-methamphetamine, there's so many impacts, aren't there? Interpretation of casework, interpretation in drug driving cases potentially. Legally, methamphetamine's just

methamphetamine.

It doesn't distinguish in the UK. So section 5A, drug drive limits, for example, still apply, whether it's L or D. But there are still going to be interpretation questions, aren't there, about potential impairment and things like that. So I do think it's something we do need to think about.

And also on a side note, as was touched on in the Icelandic paper where they looked at the enantiomers of amphetamine, D-amphetamine is what's prescribed as ADHD medication. So that's also another angle that being able to distinguish between actual prescribed amphetamine versus illicit amphetamine would be quite handy in some cases. I think that can be done for ketamine as well. And you open up a whole can of worms of all the different enantiomers and all the different types of drugs.

Yes, yeah, and that's completely fair. We've been focusing on methamphetamine this episode, but actually you're absolutely right. So many drugs are chiral, amphetamine, ketamine, citalopram, some of the synthetic cannabinoids. There's all sorts of drugs out there that are chiral that exists as multiple enantiomers and we measure them as one thing and we stick our fingers in our ears and pretend that we're measuring the right thing.

But actually we don't really know. It's generally assumed a lot of the time that it is a mix of L and D, but actually it isn't necessarily as the Icelandic paper in particular really showed. I think there's been some changes as well in terms of trends. The amount of D and L methamphetamine you get in your final product when these things are synthesized depends on the synthesis pathway and the enantiomer of your precursor.

And I think there have been some changes in the last few years of international control, trying to control one particular precursor and this leading to illicit manufacture to move towards other routes of synthesis which might change those ratios. So I do think this is something we need to think about. Let's look at that 20% rule then for a minute because this paper that looked at that 20% rule was fairly old paper, wasn't it? And I believe the 20% rule is still in use in the US.

These Icelandic findings possibly bring that little bit into question, don't they? This does all make me want to set up some chiral methods and start looking at our methamphetamine cases in more detail, just to check that we aren't missing some nuance. Yeah, I think it'd be really interesting to see what's out there at the moment, whether there is more D than L, whether that sort of ratio is changing. Yeah, and potentially significant interpretation implications.

So in conclusion then, methamphetamine isn't necessarily what we think of when we think of methamphetamine. The different forms of methamphetamine can have very different effects and actually possibly what's being sold on the street is not the form that you think it is. So I hope you've enjoyed listening this week. Do give us a like and follow on social media.

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