

Episode 29: Delta-8 THC vs Delta-9 THC - How One Double Bond Alters Clinical Effects

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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 looking at delta-8 THC which is a cousin of the more familiar delta-9 THC.

There's not a lot between delta-8 and delta-9 chemically, is there, only a double bond. What's your favorite double bond? I don't think I have a favorite double bond. Completely reasonable.

I'm nerdy but I'm not that nerdy. The position of double bonds in molecules is a bit like the positions of commas in sentences, isn't it? It can completely change the meaning of a chemical by moving a double bond in the same way that "let's eat, granny" versus "let's eat granny" are two different sentences. Before we jump into today's episode I just want to thank all of you for listening.

We recently hit a thousand plays on the podcast and so we're really grateful for anyone who's listened, shared, liked, followed. It means the world to us, it really does. If you want to keep up to date with our latest episodes you can find us on socials, so you can find us on Instagram at @the_tox_lab. We also have a LinkedIn page and for those of you who don't use social media but want to get in touch with either feedback or suggestions for future episodes you can email us at thetoxlab@gmail.com and these details are in the description below.

So what is delta-8 and how does it compare to delta-9? Historically cannabis used to be simple, didn't it? It used to be a psychoactive plant that had an amount of delta-9 THC and it contained a whole host of other cannabinoids but not a lot was known about them and in general people didn't really seem to care. And then more recently we've had movements towards CBD farming and CBD products, so cannabidiol is another cannabinoid, and then from there we've seen this rise of semi-synthetic cannabinoids, so compounds that are chemically altered versions, usually of CBD.

But we've talked about this before haven't we? I think we've mentioned it a couple of times on various episodes about semi-synthetic cannabinoids and delta-8 is essentially one of those. It does occur naturally in very low concentrations, actually, in cannabis plants it has been detected, but more often than not it's being seen through the chemical alteration of CBD. Chemically it's an isomer of THC, the only difference is that the double bond is in a different place.

So this week we're going to look at a couple of papers. One is a controlled study of delta-8 and one is a clinical case report. Rebecca why don't you dive in with the first paper. So this study looks to compare the acute effects of delta-8 THC versus delta-9 in healthy adults who infrequently use cannabis.

This group looked at both oral ingestion and vaporized routes but the paper we're going to talk about today is the oral ingestion paper. So they recruited 18 to 45 year olds who were in general good health who had negative drug and alcohol screens before each session and admitted to using cannabis within the last two

years but not within the last 30 days.

They underwent five outpatient experimental sessions where they orally self-administered either a placebo or 10 milligrams, 20 milligrams or 40 milligrams of delta-8 THC or 20 milligrams of delta-9 and these sessions were spaced one week apart and the order was randomized so no one knew what they were getting at the time. At the beginning of each session participants were given a low-fat breakfast such as toast and jam, then they had a catheter placed in their forearm vein for repeat blood collections and they completed a load of baseline assessments.

This included a blood draw, a drug effect questionnaire, vital signs measured and they underwent tests to assess their cognitive and psychomotor performance. Then this bit made me chuckle I'm not entirely sure why but it was really funny that they then gave each participant a Betty Crocker fudge brownie mix brownie that had the measured dose of THC in it. Shout out to Betty Crocker. I mean it's a great brownie mix if anyone's not tried it I highly recommend if you're like in a pinch and just really fancy some brownies because they are really really good.

Sponsorship positions are available and then after this they had bloods and repeated these tests at set time points. So a little look at the tests they were conducting: they all participated in a drug effect questionnaire where individuals answered between zero and a hundred, so not at all to extremely, on questions related to the overall magnitude of effects, so how the drug made them feel, positive effects, negative effects and then perceived impairment. Then they underwent four different tests to assess psychomotor performance, working memory, divided attention and global impairment.

This also covered balance and reaction time and higher-order cognition and heart rate and blood pressure were also monitored. So 19 individuals took part in this study, 12 men and seven women. Average age was 28 years and the average weight was 79 kilograms and 67 days on average had passed since their last cannabis use.

It's important to mention that six adverse events rated mild to moderate were found in the study, two individuals found the IV catheter uncomfortable, nausea and dizziness was reported in two after ingesting delta-9, dizziness and headache was reported with placebo in one individual and lightheadedness and dizziness was reported at a 10 milligram delta-8 dose. Hard to read very much into that, isn't it? Given that the placebo and the delta-9 group all seem to have similar experiences. Yeah exactly and they all resolved with very minimal treatment, no one dropped out of the study because of these adverse effects and it's important to mention.

So with both delta-8 and delta-9 THC, concentrations peaked in both parent drug and metabolite between two and four hours after ingestion and steadily decreased over four hours. When looking at ratios of parent drug to metabolite the ratio of delta-8 to hydroxy-delta-8 was higher than with delta-9 and its hydroxy metabolite, but the reverse was found when looking at the carboxy metabolite so there was a lower ratio of delta-8 to carboxy than with delta-9.

That's interesting so that does suggest some differences in metabolism, delta-8 versus delta-9, although they seem to follow the same metabolic pathways perhaps they've got a preference of one over the other, interesting. So with a 40 milligram dose of delta-8 and a 20 milligram dose of delta-9, subjective ratings of drug effect, misuse liability and common sensory effects associated with acute exposure were all high. At 20 milligrams of delta-9 there were high subjective ratings for drug effects and they described these as feeling high, anxious, nervous and dry mouth compared with any of the delta-8 doses.

Interestingly they saw no significant differences between the 40 milligram delta-8 dose and the 20 milligram delta-9 dose or the 10 milligrams of delta-8 and the placebo. Okay so 10 milligrams possibly wasn't doing very much but it was dose dependent within the delta-8 group beyond that. Yes. Forty was considered stronger than 20.

Yep. In the psychomotor tests 40 milligrams of delta-8 and 20 milligrams of delta-9 THC both showed a low number of correct responses on tests associated with psychomotor performance and heart rate was significantly elevated in both the 40 milligram delta-8 group and the 20 milligram delta-9 group relative to placebo. What was also interesting was that with a 20 milligram dose of delta-9 the heart rate increased

more than both the 10 and 20 milligrams of delta-8. So it kind of suggests in their conclusion for this paper was that delta-9 is more potent than delta-8.

So at least looking at oral ingestion it looks like delta-8 is probably a bit less potent than delta-9 in terms of drug-impairing effects. Not a lot more we can say is there. Relatively small study although I think quite well performed to be fair. It was. They do mention that with the study they couldn't detect differences in sex and other factors associated with the individuals just because of how small their population was and they were also only looking at a single edible formulation.

So things like gummies or drinks and things like that might have different effects versus THC baked into a brownie. Yeah and crucially as well this was effectively pharmaceutical-grade delta-8 THC. Yes they also mentioned that there was no CBD or anything in there that could cause any other interactions so that all plays a role when looking at this. Alright so let's now move on to the case report.

So a previously healthy two-year-old girl was transferred via air ambulance after being found with reduced responsiveness and sedation after reports of CBD edible ingestion. Forty-five minutes prior to arrival at her local hospital she was found with a GCS of 3 and was minimally responsive to stimuli. She was 15.3 kilos, had a heart rate of 136 beats per minute and her oxygen saturation was 98%. Due to the acute encephalopathy and concerns about protecting her airway she was intubated using ketamine and fentanyl.

After arriving in hospital she remained minimally responsive but with spontaneous eye-opening and upper extremity movement and she was given a dexmedetomidine drip for light sedation and was admitted to the pediatric ICU. So this is quite a textbook clinical presentation of cannabis ingestion isn't it in children. A loss of consciousness but actually not a collapse of respiration which is actually fairly unusual. So after speaking with the family it turned out that the father had purchased delta-8 THC gummies from a local gas station and the packet contained 12 gummies each with a dose of 25 milligrams of delta-8 THC.

They found their daughter behaving oddly and lethargic and then came across the open packet which was empty and three of the gummies were still on the floor. So they assumed that she had ingested the other nine gummies which equals a dose of 225 milligrams of delta-8 THC which is 14.7 mg per kilo. So quite a decent dose. So let's compare that quickly to the previous study.

The last study they were ingesting a maximum of 40 milligrams and two-year-olds are quite a bit smaller than adults. So they sent samples for toxicology and the samples were screened using an enzyme-linked immunoassay of the urine sample which was positive for cannabinoids and fentanyl which isn't surprising because fentanyl was given. LC-MS was reflexed based on this and fentanyl was found at a concentration of 5 nanograms per millilitre and the carboxy THC was greater than 400 nanograms per millilitre. Samples were also tested via GC-MS which detected ketamine, fentanyl and cannabinoids.

And I don't think in this lab they were able to differentiate between delta-9 and delta-8 THC. So samples were sent to the DEA toxicology testing program where they used LC-QTOF-MS and confirmed the presence of delta-8 but no delta-9. In plasma the delta-8 concentration was 107.6 nanograms per millilitre and the carboxy THC was present at 746.5 nanograms per millilitre and in urine that carboxy metabolite was present at 1550 nanograms per millilitre. It's all fairly high.

Let's drill into the testing aspects of delta-8 versus 9 for a moment because I think this is quite an important area. Really there's two ways of testing for cannabis exposure isn't there? Either immunoassay which detects the presence of a compound with a shape like delta-9 THC or you've got mass spec which measures the mass of the compounds and both are going to be affected by delta-8 in different ways aren't they? Delta-8, as we said at the start, there's only a very slight difference, a double bond is moved.

If you're using immunoassay as they were initially as the screen in this hospital you might get some cross-reactivity but I don't think we really know how much cross-reactivity you get. It may not be like-for-like the same as delta-9 so if you're using cutoffs and things like that there's a chance that your screen is either going to miss it or overestimate it. Conversely if you're doing mass spec analysis because delta-8 and delta-9 have got an identical mass it really is going to depend on your chromatography. If your chromatography doesn't separate them you may not know the difference.

If it does separate them and you're using automated peak integration and things like that the software might not even see the peak, you might not even get a positive hit on your mass spec. So I do think that expanding our testing to make sure we're covering delta-8 actually is something that labs do need to be thinking about. So luckily the story has a happy ending. She was extubated 10 hours after her admission to the pediatric ICU, was monitored for 24 hours and her GCS had returned to normal and any mental impairment had resolved 24 hours later.

So you mentioned there Rebecca that this was purchased at a gas station, this is a US case report. What's the legal situation in the US? This is definitely a loaded question. So in 2018 US Congress passed the Agricultural Improvement Act, also known as the Farm Bill, which removed hemp and its derivatives, which was defined as cannabis containing less than 0.3% delta-9 THC, from being a controlled substance.

So delta-8 was then legal and then we saw an increase in issues. In 2023 there was a national survey of 12th graders so these are children aged between like 17 and 18 and 11.4% of them had admitted using delta-8 in the last year. This was either for recreational use to self-treat conditions such as depression, insomnia or pain relief and there were legal advantages over using traditional delta-9 THC. I'm not a legal scholar and I'm definitely not a legal scholar of US cannabis law.

I think it varies by state as well doesn't it? It does which just makes the whole thing a lot more complicated. At least in certain states due to these legal changes there has been this rise hasn't there of semi-synthetic cannabinoids. They're not delta-9, therefore they're not controlled.

We spoke a few weeks ago didn't we about mitragynine products being sold freely and some of these delta-8 products, it's very similar isn't it? The presence of gummies and edibles and vape cartridges and yet clearly, you know, quite psychoactive and in the case of this case presentation actually could potentially have caused harm. Gummies in particular are a problem for children aren't they because they look just like sweets. Yeah I think it just highlights the dangers of having recreational drugs in these sorts of formats and the importance of just keeping them out of the way.

I think you just throw them on the table without a second thought but a two-year-old is going to see a packet of sweets and think I'm going to open them and give them a try. Potentially even with a childproof cap, I know from my experience childproof caps are not childproof. The legal landscape in the UK is very different isn't it? Delta-8 is officially controlled under the Misuse of Drugs Act as a positional isomer of delta-9.

We do still see it though don't we? It is still listed for sale on certain websites claiming to be able to ship. We do still see occasional American imports making it through the border onto the street and it is increasingly, I think, making cannabis testing more complicated for sure. I think the picture across Europe is very similar as well, some countries have outright banned it, others are stuck in this sort of legal grey zone.

So what do we think? Do we think that delta-8 is milder than delta-9? Is that our conclusion? Potentially at least as far as oral ingestion is concerned the group that we looked at at the beginning who looked at delta-8 and delta-9 ingestion in brownies also looked at the differences between vaporizing delta-8 and delta-9 and when you vaporize it delta-8 elicits a comparable psychoactive effect to delta-9 and considering we believe that delta-8 is slightly less potent this might be just due to differences in routes of ingestion.

Okay so yes it's possible that the first study then actually the difference between delta-8 and delta-9 was more to do with its absorption and metabolism potentially rather than necessarily it being less psychoactive. It's certainly marketed as being a milder version. If you look at the various websites selling delta-8 they do claim that it is milder than delta-9, it may be entirely subjective, maybe we need more research.

And interestingly both with the oral ingestion study and the vaporized study there was less psychoactive 11-hydroxy metabolite of delta-8 present in comparison to delta-9 so I don't know whether that might help to account for the differences in psychoactivity. Differences in metabolism of the two compounds might influence it a bit that's a good point. It's clearly not a safe compound though is it? I mean look at that case report and as I say that presentation really was classic cannabis ingestion in a child except it wasn't traditional delta-9, it was delta-8.

I think this is where the testing thing does worry me a bit, we do need to make sure that we are able to test for it. If delta-8 and delta-9 do have different potencies we do need to be able to tell them apart in order to have any hope of actually interpreting some of this. There's going to be big implications for other areas as well isn't there? Outside of clinical toxicology like road impairment, driving under the influence and drug cutoffs, the section 5A legislation specifies delta-9 not delta-8.

There's a lot of legal catching up that needs to be done and also labs do need to be picking this up. Another thought I have got with this: if delta-8 is actually milder than delta-9 are users just going to take more of it to get the same sort of effect that they're used to. Possibly if they're after that classical delta-9 effect then they are gonna keep redosing until they get there. We're in sort of a weird place ethically aren't we?

Not so much us as toxicologists but the whole market in general. You've got a drug which is really well studied but controlled, delta-9, and then you've got a completely untested version that has similar effects and that's being sold completely legally despite the fact there's been no testing or very limited research. It's a very very odd situation to be in. We would really like to hear from some of our colleagues in the US actually as to how they're dealing with this because they're going to be seeing a lot more of it than we are over here.

So let's look at the public health implications. Who's most at risk here? I mean arguably if delta-8 is less potent and there is less risk associated with it, although we don't know because it's not been as thoroughly tested as delta-9. It might be a better alternative but as of yet we just don't know.

It's really really an unknown isn't it? Your facts about how many teenagers have used Delta 8. My perspective is that there is a perception that legal or uncontrolled equals safe. Hmm.

And clearly there needs to be some balance doesn't there? What's next? I guess that's the question as always. It's a good question.

I mean I imagine at some point the UK will follow the US trend and we might start seeing more delta-8 versus delta-9 if we can test for it and labs are looking for it. Yeah it's tricky isn't it? I don't think delta-8's going away. I think that the cannabis landscape is only going to get more complicated.

We've mentioned on here before about semi-synthetic cannabinoids like hexahydrocannabinol. They're making this whole thing even more complicated because all of the logic we've just applied to delta-8 and delta-9 in terms of testing. Again, same if you're using immunoassay screening, you might not pick these compounds up or you might but we don't know to what extent. And if you're using a mass spec you need to make sure you're looking for it on your mass spec.

I think really the whole cannabis landscape has just got so much more complicated in the last few years hasn't it? Really we've gone from... Yeah cannabis being cannabis. Cannabis being cannabis.

Cannabis coming in two flavors. Weed and hash. And now it's everything in between and you've no idea what actual cannabinoids are in there. Okay so in conclusion cannabis has become more complicated.

The presence of delta-8 is starting to emerge in clinical toxicology and we're really just scratching the surface of what we really know about some of these newer compounds, these newer cannabinoids. So I think we're going to wrap it up here. I hope you've enjoyed listening to us this week. Do remember to like, follow, comment on our posts that would be great.

So 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 socials but want to get in touch anyway you can email us at thetoxlab@gmail.com. All the papers we've discussed today will be linked in the episode description below if you want to give them a read and check them out for yourselves. And again a huge thank you to all of our listeners.

We're really grateful to each and every one of you for tuning in each and every week. Hope you all have an amazing week and we'll see you next time. Bye!