THE TOX LAB

Podcast Transcript

Episode 34: Cocaine + Alcohol - Cardiac & Hepatic Consequences

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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 what happens when you mix cocaine and alcohol and why that's perhaps a bad idea. Before we get into that, Rebecca, things which are bad to mix, what's your experience?

I'm thinking orange juice and brushing your teeth, that's generally quite a bad idea. Yeah, that's quite gross. Apple slices and ketchup. Have you ever done that?

Yes. Why? Was it a dare? No, with, controversially, with McDonald's ketchup, because it's a little bit sweeter, it kind of works but it doesn't work with regular ketchup.

If anyone's listening and they're currently sat in McDonald's with some apple slices and ketchup, do give it a go and let us know. It's really good. Sounds like an awful idea. But not as bad, probably, as cocaine and alcohol, right?

I feel like we've mentioned a few times over these last few weeks about how there's been an increase in cocaine and alcohol co-use together. And it's a relatively common combination that we see. People go out, they have a few drinks, they take a bit of cocaine. But I think what is often underappreciated, particularly amongst those who mix both alcohol and cocaine, is actually what's going on pharmacologically.

There's certainly a perception, isn't there, that if you have a few drinks and then you take some cocaine, it takes away some of the negative effects of the alcohol and you can drink a bit more and party a bit harder. But there's actually a unique pharmacological mechanism happening in which your body is producing a unique compound called cocaethylene. So what is cocaethylene? Well, to talk about that, we need to look a little bit at the breakdown or the metabolism of cocaine.

So briefly, cocaine has two key ester groups. It has a methyl ester and a benzoyl ester. And normally, the breakdown of cocaine is that esterase enzymes break down the methyl ester and produce benzoylecgonine, which is the metabolite we're probably all familiar with. The hydrolysis of the benzoyl ester produces ecgonine methyl ester, which is another metabolite we may have heard of.

In the presence of alcohol, however, something strange happens. The liver kind of goes rogue and a transesterification happens. And this replaces the methyl group on the cocaine with an ethyl group. And this leads to the formation of cocaethylene.

So cocaine and alcohol together, you get formation of cocaethylene. Right. Why do we care? Well, cocaethylene, unlike benzoylecgonine and ecgonine methyl ester, cocaethylene is pharmacologically active.

So it blocks dopamine reuptake just like cocaine. And so the user still gets that surge of euphoria, energy and confidence. The difference, though, is cocaethylene actually hangs around a lot longer. Its half-life is

about double that of cocaine.

Cocaine famously has a short-lived high. Cocaethylene hangs around much longer. This can feel like a good deal to users, right? Suddenly they're getting a lot more out of their cocaine.

But it does mean the crash can be a lot harder. You can get a delayed peak. But not only does it hang around longer, but it's actually way more toxic. And that's what we're going to be looking at today.

Before we jump into today's episode, if you want to stay up to date on our content or want to get in touch with us, you can find us on Instagram at @the_tox_lab. We also have a LinkedIn page. And if you don't use socials but still want to get in contact, you can email us at thetoxlab@gmail.com. So let's zoom in on the heart and look at our first paper.

So this first paper is a systematic review of cardiovascular risks of simultaneous use of alcohol and cocaine. So as some of you may know, cocaine is a potent, sympathetic drug and causes considerable cardiac complications, including coronary vasospasm, myocardial ischemia, acute MI, cerebrovascular disease, ventricular arrhythmias, and can also cause sudden cardiac death. In 2011, the drug abuse warning network in the US stated that cocaine led to 40% of all drug-related emergency department visits, and alcohol was responsible for 29% of all the cocaine-related visits, which equates to 174,000 emergency department visits in that year.

So this literature review covers 42 studies looking at the differences in cardiovascular effects when using cocaine and alcohol together versus cocaine on its own. So cocaine can inhibit reuptake and increase receptor sensitivity of noradrenaline, dopamine, and serotonin. It can act to increase heart rate, blood pressure, and myocardial contractility, which increases the oxygen demand in the heart. The increase in noradrenaline can also cause vasoconstriction, and along with its prothrombotic effect, can decrease oxygen supply to the heart.

So that's a bad combo because you need more oxygen, but you're not able to deliver that. And when demand of oxygen exceeds supply, you can get effects such as ischemia or infarction, which may lead to acute MIs, and that's the most frequent severe complication associated with cocaine. You can also get alterations in sodium and potassium channels in the heart, which can lead to effects such as QRS widening and QT prolongation, which may lead to arrhythmias.

So alcohol use on its own only slightly increases heart rate, blood pressure, and cardiac output, but when the combination are used, you produce a significantly higher increase in heart rate, which causes an additional increase in myocardial oxygen consumption. When used together, alcohol can lead to a significantly higher plasma concentration of cocaine, and it's thought to be due to a faster rate of absorption or inhibition of hepatic cocaine metabolism. And when cocaine and ethanol are used within two hours of each other, you get the formation of this product, cocaethylene.

And this induces similar cardiac effects to using cocaine alone, but has a plasma elimination half-life of about two hours, which is between two and five times that of cocaine. Cocaethylene is also a more potent blocker of those cardiac sodium and potassium channels, which can increase the cardiotoxicity of using cocaine. When looking at cocaine-related emergency department presentations, the presence of cocaethylene related to higher rates of cardiac arrest and raised lactate. But interestingly, there was less myocardial injury present based off measurements of troponin.

In a study of 471 trauma patients, the presence of cocaethylene was associated with a five times higher risk of requiring intensive care. When looking at cocaine-related mortality statistics, death was frequently caused by cardiac failure, and the combination of cocaine and alcohol was the second most common drug combination in fatalities behind cocaine and heroin. When you say it like that, it does make you wonder if users knew that, whether they changed their behavior, right? Possibly.

And when looking at the levels of cocaine in these cases, the level of cocaine when in combination with alcohol was a lot lower than when deaths occur through cocaine use alone. So it does suggest there is quite a significant pharmacological effect contributing, because otherwise you wouldn't expect patients with these cocaine concentrations to actually be presenting to hospital, is what you're saying. Yeah. And these are

death-related stats.

Oh, these are deaths? These are death stats. Okay. One interesting fact I did find with this paper was that in 2022, 22% of all cocaine-related death in England and Wales had alcohol present, and I was expecting it to be a lot higher than that.

22% of deaths involving cocaine had alcohol present. But I bet quite a lot of them had other drugs present too, if not alcohol. This is probably true. Probably got some bias in the population there, haven't we?

I'm surprised it's not higher than that though. Yeah, that's my point. So clearly we're seeing an increased risk, aren't we? Yeah.

Cocaine and alcohol makes things quite a bit worse in the cardiac setting and in the fatality setting. Interestingly, 22% of cases detected alcohol and cocaine together. How many of those actually reported cocaethylene? It's not necessarily something everybody is screening for.

For example, clearly there's a value in actually understanding its presence. Yeah, I think especially with patients presenting to emergency departments, having that and the understanding that that could increase the risk of arrhythmias could be useful. Yeah, I can see that. I do think it's really under-appreciated phenomena, particularly amongst people that will go out on a Friday and have a few drinks and have a few lines.

We know cocaine carries with it increased cardiovascular risk anyway, but the fact that this effect is magnified with alcohol I think is perhaps under-appreciated. Okay, so that's the cardiac effects. Now we've got another paper, haven't we, looking at some liver effects. So why don't you take us through that?

So this paper gave me really bad flashbacks to my undergraduate degree when I was doing a lot of mitochondrial protein analysis and looking at damage to mitochondria and things like that. So we'll try and take it through step by step. So cocaine has been shown to activate components of the immune response, trigger cytokine processes, and alter cellular homeostasis in the liver, heart, and brain. It can also promote oxidative stress, which leads to the production of reactive oxygen species, which can lead to inflammation, and this can happen in the liver.

So in the liver, cocaine is metabolized to benzoic acid by cytochrome P450 3A4, and this is converted to benzoyl-CoA, which can then bind to glycine to form hippuric acid, which I'm going to refer to from here on in as HA. And this can induce mitochondrial dysfunction and apoptosis. So the aim of the study was to look at the role of cocaine in liver injury in mice, help to identify metabolic pathways and investigate the hepatic damage associated with them. And it also aimed to examine the synergistic effects of cocaine and alcohol on liver injury.

So hit us with some hardcore biochemistry. So when mice were injected with cocaine, their average weight gain decreased. There was an increase in liver enzymes such as AST, ALT, and ALP, and significant increases of lipase and amylase were also noted. So some liver dysfunction, possibly some pancreatic dysfunction going on.

There was also increased inflammation to the liver that was noticed, and an increase in cytokine expression. So things like TNF alpha, IL-1 beta, and IL-6. On histology, they observed cocaine-induced balloon degeneration and hepatocyte death. They also demonstrated that when you give cocaine, you get a concentration-dependent increase in the production of HA.

When they gave both cocaine and ethanol to mice, they observed more severe liver damage based on ALT and AST. And there was also a significant increase in the amount of mRNA of these inflammatory cytokines. And you also got all of the hepatocyte damage that you can see on histology as well. But there was no significant increase in the amount of HA produced when combined with alcohol.

So there was no statistically significant increase in this compared to just cocaine on its own. So cocaine led to significant inflammatory changes and an increase in hippuric acid. But when mixed with alcohol, the hippuric acid didn't increase. Yep.

It didn't increase any more than it would have just with cocaine on its own. So they then went on to look at the effects on Kupffer cells, which are specialized macrophages that can be found in the liver. So within the Kupffer cells, when treated with HA, they saw a decreased expression of mitochondrial transmembrane potential proteins such as TOM40, TIM23 and HSP60. They also saw an increase in mitochondrial reactive oxygen species production and increased leakage of mitochondrial DNA into the cytoplasm.

So these are all markers for mitochondrial damage. Again, they saw an increase in the amount of mRNA for cytokines. And when treating these cells with cocaine, they saw very similar effects. They are hypothesizing that the production of HA from cocaine's metabolism is causing all this mitochondrial damage.

They also took the media that they'd been growing the cells in that they'd treated with cocaine and applied it to some hepatocytes and demonstrated an increase in hepatocyte cytotoxicity, which is probably from the increased amount of cytokines coming from the cocaine-treated cells. So as we all know, alcohol can cause liver damage. Specifically, it can impair mitochondrial energy metabolism, enhance the formation of reactive oxygen species, leading to hepatocyte cytotoxicity. And again, they demonstrated in combination with cocaine that hepatocyte cytotoxicity is greater.

Alcohol has also been shown to increase the expression of TNF receptors. And as I mentioned before, TNF alpha is one of the cytokines that's produced. So therefore, you're going to get an increase in the amount of damage that's occurring. It's interesting, isn't it?

So cocaine appears to be not only toxic to the heart, but also toxic to the liver. Alcohol, we know, is toxic to the liver. You mix alcohol and cocaine, that's even more toxic to the liver. I think that the chronic toxicity of cocaine is probably underappreciated, isn't it?

We're so often used to thinking about cocaine either its effect on people, so how it makes users feel and how it affects their driving and how it influences their behavior. We're used to thinking about how it can cause heart problems and how, ultimately, it can lead to people's morbidity and mortality through acute mechanisms. But I think the chronic effect on things like the liver is actually really underappreciated. And this study is really nice because it gives us proposed mechanism for why it can lead to this increased liver damage.

We haven't really mentioned it, but actually, the benzoylecgonine breakdown product is broadly considered inactive. It doesn't lead to the same psychological effects that cocaine does, but it is still quite hepatotoxic. And that too can increase the cellular damage on liver cells and on kidney cells. It'd be interesting to know whether the formation of cocaethylene impacts liver damage, whether that in itself is hepatotoxic or not.

Obviously, in this paper, they're just talking about how cocaine damages the liver and how alcohol damages the liver and how they kind of meet up rather than how cocaethylene might be toxic on its own. Yeah, if they're proposing their hippuric acid pathway, then perhaps it maybe doesn't. I'm not sure. It'll be really interesting to find out, wouldn't it?

So do we need better education on this combination? Probably. I don't think people fully appreciate how mixing certain things, especially cocaine and alcohol, can be damaging. Whether that would change anyone's behaviors, because cocaine is the typical party drug that you'd have when you're drinking.

Who knows? Yeah, completely fair. I mean, that's the eternal question with any harm reduction messaging, isn't it? Is it going to have an impact?

I wonder if there's enough awareness amongst healthcare professionals too. We've talked a lot in the EUDA report, didn't we, about how there were an increasing number of hospital admissions involving cocaine and alcohol. Are the combined effects recognized by people in the healthcare setting dealing with these people? And particularly with the prolonged half-life, is there a risk that we're not monitoring these people for long enough, and things like that?

That is a worry. I don't know how well recognized that sort of effect is among people who work in emergency departments. But yeah, there is always a chance that we're discharging people too early and

they're going home and having potentially fatal arrhythmias. So thinking as toxicologists, what are the implications for this?

I'm thinking we need to be reporting cocaethylene because it's relevant, particularly in light of the fact that cocaine concentrations were lower in the presence of cocaethylene in fatal cases. I'm thinking about the chronic effects of cocaine and the liver damage in particular. I don't know how well appreciated that is amongst people. I don't know how significant it really is on a population level.

That's not to say it isn't. I'm just not sure. The liver is remarkably good at healing itself, isn't it? It'd be interesting to see if there is more prevalence data that shows that cocaine use plus alcohol does lead to your long-term increases in risk.

And I wouldn't be surprised either if any liver damage picked up in this sort of population would just be put down to alcohol use rather than the combination and the fact that cocaine may have played a role in it. Yeah, that's completely fair, isn't it? Maybe just, yeah, put down to bad luck of oh, well, you've been drinking and therefore it's the alcohol. Yeah.

Okay. So in summary, mixing alcohol and cocaine quite a bit worse than mixing vodka Red Bull, you get a pharmacological interaction that actually increases your risk both acutely and possibly chronically, though we're less sure about that one. Either way, mixing cocaine and alcohol leads to increased risk, increased harm. Generally, probably a bad idea.

So I think we're going to wrap it up here. I hope you've enjoyed listening this week. Hope you all have an amazing week and we'll see you next time. Bye.