Episode 59: When Is Toxicology Biochemistry? Exploring Drugs That Alter Glucose Metabolism

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Transcript

lab. I'm Rebecca. I'm Rob. This week we're going to be taking a look at drugs which can alter glucose metabolism.

Before we jump in, how are you Rebecca? It's been a few weeks hasn't it? We've had a little Christmas break. Yeah.

Did you have a nice Christmas off? Yeah. Yeah, looks good. Lots of food.

Anything exciting happen? Well our article on protein interzine made editor's choice in the October issue of the Journal of Analytical Toxicology which was very cool. It was really exciting wasn't it? And it's now been made open access so everyone can enjoy it so if you haven't it's quite science heavy but do go and have a read.

And if you would rather not read and listen we did cover it on episode 37 of the podcast. It's a good memory that you know the number. It's quite sad actually that I know the number. So going back to Christmas other than that you had a nice time.

Lots of Christmas excesses. I wasn't too bad this year I feel like I had a decent level of self-control over the chocolates but. Other than making a massive Christmas dinner I think I was pretty reserved actually which makes a change for me. But it is a time of year isn't it where seasonal excess can lead to a bit of metabolic stress right a little bit of altered glucose metabolism and this week we're gonna be looking at glucose biology and how drugs can interact with that and really ask the question as toxicologists are we getting the full picture do we need to be thinking a little bit like biochemists as well.

Before we dive 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 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 let's start out looking at an anti-diabetic drug because as we know diabetes is a disorder of glucose metabolism, and anti-diabetic drugs help by altering those glucose pathways, and we're going to be looking first at metformin which is one of the most widely prescribed anti-diabetic drugs.

This first case covers a 70 year old male with type 2 diabetes who had been admitted to hospital for a prosthetic joint infection. He had been experiencing vomiting, painful urination and shortness of breath and subsequently developed respiratory failure which required manual ventilation and he passed away a few weeks after his admission. An autopsy five days after his death showed multivisceral congestion and pulmonary edema and there was blackish liquid found in the oral cavity, nasal cavity and the urine was also dark in color. The only other findings of note were a stereotoxic liver and the presence of a thyroid cyst.

During the autopsy they collected heart blood, femoral blood, urine, vitreous humor and gastric contents for toxicology and biochemistry tests. Glucose was measured in the vitreous humor sample and this was found to be less than 0.1 millimoles per liter and they've suggested that this indicates an

absence of hypograssemia at the time of his death. HbA1c was also measured in blood and was found at 7.7% which is 61 millimoles per mole and this is consistent with a diagnosis of diabetes and it indicates poor control. They also measured lactate in the vitreous and this is found at a concentration of 13 millimoles per liter.

However this is quite tricky to interpret as lactate increases after death in vitreous. Yeah I was going to jump in on you at that because also glucose goes down and can get converted to lactate by microbes in the sample so I'm not sure we can say conclusively he wasn't hyperglycemic at the time of death and an amount of glucose could have been converted to lactate. Beet hydroxybutyrate was also measured in both blood and vitreous humor and this was elevated but this was thought to be the result of the vomiting and insufficient food intake in the days before his death.

Metformin was also quantitated in the various fluids that they had available and this was found to be a concentration of 45 milligrams per liter in femoral blood which they've stated is within the range that may be associated with fatal toxicity but is definitely at the lower end of that range and most case reports metformin concentrations are kind of like the hundreds. Authored absorption and bioavailability of metformin can contribute to also toxicity.

They're lit to the metformin concentration in the stomach which is found to be 202 milligrams per liter and the author stated this did not suggest an excess ingestion of metformin and this may point towards instead a defect in elimination of metformin. So metformin is excreted, unchanged in the urine with a half-life about five hours. The creatinine concentration was measured in the vitreous humor and this was found to be a concentration 277 micromoles per liter which is suggestive of some renal impairment and this could have caused the elevated metformin concentration that's found in this case.

And there were definitely some signs and symptoms of renal impairment before he passed away weren't there? Very low-volume highly concentrated urine. It's a tricky case isn't it because he was actually in hospital for a while, probably hasn't taken a massive overdose of metformin but yet concentration on death was quite high but as you say not at the sort of very high end that you do sometimes see with deliberate metformin overdoses plus you've got this renal function decrease which could well be leading to increases in metformin concentration. So what's the mechanism then of how metformin is toxic?

What do we think has actually happened here? So metformin is generally quite a safe drug but one major side effect is lactic acidosis and this is considered the most serious complication. It's quite a rare complication it occurs in approximately two to nine cases per hundred thousand and the mechanism of this isn't completely understood but it's likely linked to the inhibition of gluconeogenesis.

So metformin I don't think we entirely understand how it works do we but there are some proposed mechanisms and it's believed that it interferes with hepatic mitochondrial function leading to hepatocytes liver cells essentially believing there is less energy available than there is and therefore shunting its focus away from gluconeogenesis.

So the formation of glucose from non-glucose substrates amino acids fatty acids and that's the proposed mechanism for why it causes people to have lower blood glucoses but I think it's also believed that this shift metabolic shift can lead to in some cases to an upregulation of anaerobic metabolism and therefore production of lactate. So all in all I think this is a really interesting case isn't it? You need to consider the biochemistry you need to consider the renal function you then need to consider how that could have had an impact on the blood concentrations of metformin.

I don't think we can rule out an overdose entirely on a basis of a stomach contents measurement. No. That feels a little bit of a stretch but I can appreciate that perhaps this doesn't support a very obvious huge overdose at the time of death. And so if we'd have just looked at the blood concentration in isolation and not considered the other wider biochemistry would we be jumping to the wrong conclusions here?

This next case looks at a 34 year old female who went to her doctor wanting help losing weight. She had a history of type 1 diabetes, dyslipidemia and morbid obesity and she was diagnosed with type 1 diabetes 10 years previously after developing DKA. She had been using an insulin pump for about two years but frequently skipped mealtime insulin bonuses which resulted in poor diabetes control and as a result her HPO and C was 9.2% or approximately 77 minimals per mole. She did not have a history of diabetic retinopathy, neuropathy or nephropathy and had not experienced an episode of DK since the first episode when she was diagnosed.

Her prescribed meds included insulin and receiver statin and she was prescribed 75 milligrams of diethylpropylene daily for her weight loss and she'd also enrolled in Zimbal classes as well. Ten days after starting diethylpropylene she developed nausea, vomiting and severe cramping peri-umbicular abdominal pain since this is pain around the belly button. She did a point-of-care blood glucose measurement which showed severe hypoglycemia and despite changing the site of her insulin pump and giving herself several boluses of insulin and an injection of short-acting insulin this race glucose persisted.

Diethylpropylene is an interesting drug actually it's also known as amphepromone and it's actually a prodrug for the cathinone F-cathinone which was a class of drugs we've talked about cathinones before that saw us rise in use as recreational drugs but it's not licensed in the EU but it's sometimes prescribed around the world as a weight loss drug. It's an amphetamine analogue essentially and leads to weight loss by appetite suppression. So she then presented to hospital with a BP of 127 over 72, a pulse of 109 beats per minute or a spiritual rate of 16 and an O2 sat 98% on bromair.

Physical exam showed dry oral mucosa and she was tended to palpation in the peri-umbicular area. Blood tests revealed a plasma glucose of 40 millimoles per litre, a pH of 7.32, a bicarb of 16 millimoles per litre and an anion gap of 19 millimoles per litre and urine dipstick was also positive for ketones. So classic diabetic keto acidosis picture. They did also do a chest X-ray and a CT of the abdomen but this didn't reveal any acute pathology.

After being treated for her DKA she was then transitioned back to her insulin pump and she discontinued the diethylpropylene. So what was the mechanism here then what actually went wrong? So amphetamine like compounds promote the release of noradrenaline which then suppresses appetite and leads to weight loss through activation of B2-2 adrenergic receptors in the hypothalamus.

Noradrenaline can also stimulate fat breakdown by activating B2-3 adrenergic receptors on fat cells triggering lipolysis and the release of fatty acids and these non-esterified fatty acids undergo beta oxidation to form substrates for ketone production and this increases beta hydroxybutyrate levels. The reduced insulin as a complication of type 1 diabetes further amplifies its process by enhancing ketone production and reducing ketone clearance. And it's that general counter regulatory response we talk about in biochemistry circles isn't it?

In health when your blood glucose goes down your body responds by increasing lipolysis increasing gluconeogenesis and that's exactly what we're seeing here except in the context of already existing hyperglycemia and as you say the lack of insulin just contributes further to that that fatty acid production you can get that diabetic ketoacidosis picture. There was another paper that caught my eye this week in a similar vein although it's a very very different study looking at the prevalence of

diabetic ketoacidosis in amphetamine users.

So many drugs are known to precipitate diabetic ketoacidosis including methadone, cocaine, beta blockers, thiazide diuretics, second generation antipsychotics such as lansapine and clozapine, corticosteroids, calcium urine inhibitors and protease inhibitors and the authors of this paper wanted to see whether methamphetamine also increased the risk of diabetic ketoacidosis. So they did this by analysing autopsy and toxicology case files from the forensic science service in Adelaide South Australia between the 1st of January 2019 and the 31st of December 2019 and they examined all cases where methamphetamine was detected.

94 cases were pulled out where methamphetamine was detected post-mortem and of these 11 had a history of diabetes with 6 having a history of type 1 and 5 having a history of type 2 In 4 out of 6 of the cases with type 1 diabetes, fatal diabetic ketoacidosis was thought to have occurred and this was about 67% of the samples. They did look at a control sample of cases with type 1 diabetes from 2005 to 2009 and out of 123 individuals in this a lethal DKA occurred in only 13% of cases. In other words amongst the methamphetamine users there was a much higher proportion of fatal diabetic ketoacidosis.

The age range of these cases was between 30 and 54 with a male to female ratio of 1 to 1. In the 4 DKA cases there was an average vitreous glucose concentration of 57.4 millimoles per litre and a beta-hydroxybutyrate concentration averaging 11.2 millimoles per litre. Methamphetamines concentrations in these cases ranged from 0.02 milligrams per litre to 0.48 milligrams per litre and other non-contributory toxicology findings included alcohol in one case, citalopram in one case and paliparadone in one case.

So it does seem to be that amphetamine and amphetamine like drugs can precipitate diabetic ketoacidosis in diabetics and there's a lot to unpack here isn't there? Firstly the use of amphetamine like drugs can sometimes still be used as weight loss aids and amongst diabetic individuals possibly there's going to be a bit of an over-representation of obesity and therefore perhaps over-representation of people seeking out these drugs. Less common probably with type 1 diabetes actually, you know normally we think in obesity and type 2 diabetes.

Putting our toxicologist hats back on, some really interesting nuance to some interpretation in those cases isn't there? So those fatal diabetic ketoacidosis cases that had methamphetamine present. The methamphetamine concentrations were really not that high. Certainly in the range that you see in recreational use, certainly not obvious, methamphetamine overdoses.

You can see quite wide ranges can't you with methamphetamine as people develop tolerance and yet they died of diabetic ketoacidosis. Here is the question, was methamphetamine contributory? So they did have a couple of theories in this paper. One, the use of drugs might interrupt someone's insulin administration schedule if they're type 1, which could contribute to the development of DKA.

Methamphetamine interestingly also has a direct ketogenic effect by blocking the cellular uptake of glucose and the cardiotoxicity of methamphetamine may be exacerbated by acidosis so kind of in combination with the development of DKA could lead to fatality at like lower concentrations of methamphetamine that we're used to seeing when methamphetamine is thought to be fatal on its own.

And again then it shows the importance, doesn't it, of considering the biochemical findings alongside the drug concentrations and not just interpreting either one in isolation because it's entirely possible to look at these cases and go oh they're diabetic deaths and not consider the drug use. Yeah. But actually there probably is an interaction. So we've looked at metformin, we've looked at what is

almost the polar opposite in terms of amphetamines.

Why don't we go back to looking at some other diabetic drugs? So man in his early 60s called his primary care doctor concerned after he had four positive urine ethanol tests from the city probation office despite not drinking for 10 months. He submitted a urine sample to his primary care doctor and this was tested and showed no urine ethanol or ethyl glucuronide which is in the tablet. He did have glucose present in the urine and this was a result of his impact of frozen therapy which is an SGLT2 inhibitor and this had been prescribed five months earlier for his diabetes.

There was no elevated nitrate or leukocyte estuaries levels and urine cultures showed less than 50,000 colony-forming units per millilitre. After a call to the probation office it was discovered that urine samples were sent once a day to an external lab and these were not refrigerated. The sample that was taken in primary care was then removed from the fridge and tested for ethanol 24 hours later after being sat at room temp and then it tested positive.

The cause of this was likely microbial fermentation of the glucose in the urine into ethanol and this is a really important complication of SGLT2 inhibitor therapy that should be considered as this class of drugs causes glycosuria and increases the presence of microbes in the urine retract. Yeah this was a really short and sweet letter to the editor wasn't it in a journal but it really caught my eye. So this class of drug they help diabetes by lowering the renal glucose threshold and so people excrete glucose in their urine when they wouldn't normally and it as a result lowers your blood glucose.

As a knock-on effect urine then contains an awful lot of glucose. How is alcohol made? Alcohol is made through fermentation usually through yeast but actually bacteria can ferment glucose to alcohol too and so in this case we believe the high glucose concentration was leading to this false generation of alcohol but I wanted to look at this case a little bit because it wasn't a false positive analytically. There was genuinely ethanol in these samples the thing that went wrong in these cases was the interpretation and again it shows how you need to consider the biochemistry in order to actually then interpret the toxicology.

We do see cases like this from time to time don't we were very very high urine glucose is leading to false positive ethanol and you can sometimes get a clue actually if you're analyzing these because they fizz when you take the lid off. Interesting. Which yeah sounds a little bit bonkers but because the fermentation has actually happened within that vessel the vessel becomes pressurized. If you're ever analyzing a urine sample and it fizzes when it take lid off consider that as a possibility.

I think these are all really interesting papers aren't they looking at the interactions between toxicology and biochemistry and I appreciate I'm quite privileged because I've got a biochemistry background and I can kind of sit between the two. Is there enough biochemistry teaching in toxicology and vice versa? Or to put it another way could you have interpreted these cases correctly having only viewed it through one lens?

I think you need both sides to fully understand what's going on in all of these cases I don't know as a biochemistry I don't know how much biochemistry in general toxicologists get taught in these sorts of contexts and whether that knowledge is there. We are really privileged of our background and where we sit with these that means that we can kind of appreciate both sides of it. I guess the next logical question from that is where does toxicology end and biochemistry begin? I think it's just a very blurry messy line isn't it?

Definitely yeah I think definitely a little bit to take home there isn't there in terms of considering the biochemistry of a case. Obviously not all drugs alter biochemistry in this way but for some that do there is potentially an area of consideration that needs to be made.

I think also with the urine ethanol case it highlights the importance of pre-analytical variables and how storage conditions can really have an impact on the results that you get and knowing what's happening to your sample before you get it is really important to kind of lead you down whether certain artifacts could be happening that could alter the interpretation of your case. Yeah that's a good point because it wasn't just he was on this anti diabetic drug it was also that the samples were being stored at room temperature and there was a bit of a delay before analysis and so it was classic many holes in the cheese all lining up wasn't it?

Yeah but you know let's not ignore the potential implications here. This was a probation case you know there could have been significant impact on livelihood and future and so on as a result of this error essentially at least in terms of interpretation. Yeah and especially as it happened like four times in a row if you're looking at that that he's had four positive urine ethanol as you might think that he had been drinking and that can have some very serious consequences down the line. Well that's the crucial thing isn't it as I say the lab wasn't wrong it's just the interpretation you couldn't take it to mean he had been consuming alcohol.

So I guess one big final question then if a drug never reaches a toxic level but it kills someone by disturbing metabolism is that a toxicology problem or a biochemistry problem? Ooh both. I hope you've enjoyed listening to us this week it's great to be back after a Christmas break if you're new here you've just joined us in the last few weeks or you've been with us the whole time thank you very much for tuning in listening we do really appreciate it. Hope you all have an amazing first week of 2026 and we'll see you next time bye