Episode 69: Alcohol - Fatal Complications of Chronic Misuse

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Transcript

Hi everyone, welcome back to The Tox Lab, I'm Rebecca. I'm Rob. This week we finally come to talk about something which I'm surprised it's taken us this long to talk about, to be honest. And that is, I would estimate the drug that most of us are most familiar with, and a vast number of people use it socially, and a vast number of people don't really come to any long-term harm, but then a significant chunk of people also do.

We're of course talking about alcohol, but it's often said, isn't it, that alcohol, if it was discovered today, wouldn't be allowed to exist because of the harms associated with it. And it is fair to say that it is responsible for an awful lot of deaths globally every year. So Rebecca, when you think about deaths due to alcohol, what do you normally think about? How do you imagine it looks?

I mean, I guess the first thing that always jumps to my mind is liver failure as a result of alcohol misuse. Yeah, that's fair. So liver failure, and then you can see increases in cancer risk. Alcohol can really increase your risk of quite a few medical conditions.

But this week we're taking a slightly unusual look. We're going to be looking at three case studies, and all of them are deaths due to chronic alcohol use, but perhaps by mechanisms people are less familiar with. 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 page on LinkedIn and we're fairly active on there.

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 thetoxlab@gmail.com. So Rebecca, why don't we dive right in for this case and we can unpack it as we go along. So a male in his early 40s with a long-standing history of heavy daily alcohol consumption presented with a four-day history of progressive neck stiffness and shoulder discomfort. The patient was found on the floor of his home, unable to get up, and was taken to the emergency department.

The patient was conscious, but exhibited marked generalized weakness. He had significant neck stiffness, which was put down to a localized muscle injury rather than being a symptom of meningeal irritation. Laboratory findings showed a markedly raised AST, ALT and gamma-GT. He also had low potassium, chloride and phosphate and a markedly raised CK.

Glucose was also elevated as well as his CRP. Should we unpack these acronyms just a little bit for our less familiar listeners? So AST and ALT are liver enzymes, as is gamma GT, these are markers of liver disease. They tell you slightly different things and I don't want to get too hard into biochemistry for this episode, but gamma GT in particular you often see high in alcohol use.

And CK creatine kinase is another enzyme. This is a marker of muscle damage. So that being up indicates there's something going on with muscles. He was diagnosed with hypokalemic rhabdomyolysis and was given an electrolyte replacement including an infusion of IV potassium.

18 hours after his admission the patient went into cardiac arrest and could not be revived despite resuscitation efforts. A forensic autopsy was carried out 12 hours after death which showed a concentric hypertrophy of the left ventricular apex of the heart and an enlarged liver with fatty

changes consistent with chronic alcohol misuse. Toxicology was also completed with no drugs or alcohol present. Histological examination of the skeletal muscle showed widespread myofibronecrosis, fragmentation and inflammatory infiltration which is consistent with diffuse rhabdomyolysis.

There was also no evidence of myocardial infarction or myocarditis but there was mild interstitial fibrosis and myocardial fibre disarray. So really in essence his skeletal muscles were breaking down. Yeah. Immunohistochemical staining showed that myoglobin was present in the distal renal tubules which is consistent with myoglobin cast nephropathy.

The liver exhibited diffuse macrovesicular steatosis with moderate portal inflammation and moderate fibrosis. So the renal casts thing is essentially muscle proteins, the myoglobin clogging up the kidney tubules leading to renal disease and the liver you described is really consistent with long term alcohol use isn't it? Steatosis is increased fat. So rhabdomyolysis can be caused by a lot of things but severe hypokalemia is one of the rarer causes and it's thought that this has occurred secondary to chronic alcohol abuse in this case.

So a low potassium can cause blood vessels to constrict rather than dilate during muscle contraction which can lead to ischemia of the muscle and then muscle cell death. The low phosphate in this case might have also contributed towards ATP depletion and that may have increased the patient's vulnerability to muscle necrosis. The low phosphate is interesting actually isn't it because you often see a higher phosphate as the muscles start to break down. So he must have had chronically very low phosphate.

A low potassium can also precipitate malignant ventricular arrhythmias and the hypertrophy and myocardial fibre disarray of the heart is characteristic of apical or hypertrophic cardiomyopathy which can increase the risk of ventricular arrhythmias and therefore alongside the low potassium in this case could have precipitated a fatal arrhythmia. And I think we'll come back to the alcohol and arrhythmia point a bit later on, won't we? How low was his potassium? I'm not sure you said.

1.4 which is ridiculously low. I'm not sure I've ever seen one that low actually. I don't think I have either. And so why was it so low in this case?

Did they propose any mechanisms? I think they put it down to chronic malnutrition. Yeah that's sadly a pattern we see from time to time really with chronic alcohol use isn't it? Individuals whose entire daily calorie intake comes exclusively from alcohol rather than food.

And as a result there's no electrolytes going in, no sodium, no potassium. There's lots of calories, there's water, there's just no electrolytes. But this is a particularly unusual presentation isn't it? The rhabdomyolysis but it clearly can be a thing particularly in the context of electrolyte disturbances.

And that's a common theme with alcohol as I said. It's something that can lead to all sorts of metabolic abnormalities and they in turn can have these downstream consequences. So why don't we turn our attention now to another case? A 49 year old female presented to the emergency department via an ambulance and her son had reported that she had been experiencing diarrhoea and vomiting for two days which had resulted in her becoming confused and she had also developed slurred speech.

She had a complex past medical history including gallstones, gastritis, hypomagnesemia, so low magnesium, alcohol related chronic liver disease, GERD, both acute and chronic pancreatitis, alcoholism, IBD, migraines, benign, proxisomal, positional vertigo, all thrash, tinea, menorrhagia and anxiety. She lived alone and required a wheelchair to mobilise and she was known to drink approximately two bottles of wine a day for many years and she also smoked approximately 30 cigarettes a day. On arrival to the emergency department she was hypotensive and hypoglycemic with a glucose of 1.8 millimoles per litre.

She was given IV fluids to treat what they thought was gastroenteritis. The hypoglycemic was resistant to multiple treatments including oral, intramuscular and intravenous therapies and the fluid resuscitation only mildly improved her hypotension. Her gas analysis revealed a metabolic acidosis with a raised lactate of 6.8 millimoles per litre and a lobe by carbonate. She then went on to develop an urea which is low or absent urine output and had signed the fluid overload which suggested renal failure.

Blood tests showed low sodium, potassium and magnesium, a raised creatinine at 189 millimoles per litre and a raised urea at 15.2 millimoles per litre. Her liver enzymes ALT and AST were elevated twice and three times the upper limit of normal respectively and her bilirubin was also elevated at 45 millimoles per litre. So bilirubin is the hemoglobin breakdown pigment that turns people yellow when their liver fails so an increase in bilirubin consistent with a degree of liver failure. Dark stools were also noted and an endoscopy was considered but she was too unstable for imaging or endoscopy as this was not performed.

She sadly continued to deteriorate and died later that evening. A post-mortem examination was performed 19 days after death and internal examination revealed cirrhosis consistent with alcoholic liver disease, sclerosis, pancreas, pulmonary edema and bilateral pleural effusions. Thermal blood was taken for toxicology which showed a paracetamol concentration of 54.9 milligrams per litre. Amatrypsilin and its metabolite naltrypsilin were also detected but these were at therapeutic levels and morphine, midazolam, the pyramide and andanestron were also detected and this was consistent with her hospital therapies.

Also worth noting was that ethanol was not detected in this case. There is a lot to unpack in this case isn't there, there was a lot going on. A few things I want to drill into and see whether we can't maybe explain them or possibly not. That glucose was exceptionally low.

So one effect of chronic alcohol use can be a failure of the counter regulatory system. The liver is responsible for generation of glucose from non-glucose substrates and it is possible for someone to lose the ability to maintain a blood glucose. But in this case this is exceptionally low and they were giving her IV dextrose and it didn't seem to improve. Which is weird.

Yeah that's really unusual. The other slightly unusual thing or rather it's not an unusual thing but it's unusual that they didn't measure it is they didn't seem to measure her beta hydroxybutyrate. Now alcoholic ketoacidosis is another metabolic abnormality you can see in the context of chronic alcohol use and part of it is related to the liver's inability to undergo that counter regulatory response to respond to low glucose is by generating glucose.

Partly because the livers ran out of glycogen, partly because there's less functional liver to actually generate glucose from non-glucose substrates but also the detoxification of alcohol can deplete one of your enzyme co-factors and it can alter your metabolism effectively which can lead to this increase in ketones and produce this acidosis. Now this patient was acidotic, they did have a high lactate, I wonder if as well their ketones might have been high. Yeah no possibly it's annoying they didn't measure it but I think she went downhill quite quickly so.

Yeah that's fair enough and again yeah it's a complex story isn't it, complex background but not an uncommon story really, somebody with a lot of chronic health conditions related to alcohol sadly goes downhill. So probable cause of death proposed included hypovolemic shock secondary to fluid loss compounded by hepatic and renal dysfunction. It was also noted that while drug levels were not in excess the liver disease may have impaired the metabolism of these drugs and the cause of death was A. multi-organ failure B. pseudam and C. liver cirrhosis.

So pseudam is the sudden unexpected death in alcohol misuse and it refers to cases where an individual with a history of chronic or excessive alcohol consumption dies unexpectedly and no clear anatomical or toxicological cause is identified. Pseudam often affects adults aged between 35 and 55 with a long history of heavy alcohol use and while in these cases there are often histopathological findings such as hepatic steatosis, mild chronic pancreatitis, renal tubulin injury, myocardial fibrosis and gastritis these do not fully account for the death.

Proposed mechanisms of pseudam include cardiac arrhythmias arising from electrolyte imbalances such as hypermagnesemia and hypokalemia so low magnesium and low potassium as well as myocardial changes induced by alcohol and autonomic dysfunction and QT prolongation can further increase the risk of sudden cardiac death. Thiamine deficiency which is often associated with alcoholics due to poor nutrition and reduced liver stools can exacerbate neurological and cardiac dysfunction.

Metabolic disturbances like hypoglycemia and lytic acidosis are also thought to be a contributory factor and it's worth noting that this patient had many risk factors including chronic alcohol misuse, malnutrition, recurrent pancreatitis and significant metabolic and electrolyte abnormalities.

I'm still slightly annoyed about the beta hydroxybutyrate because I think we need to rule out ketoacidosis first before we can call it a sudden unexpected death in alcohol misuse but you've summarised it really well, it's not one thing it's probably lots of things and precipitated by an event but on a background of many, many risk factors and complex metabolic disturbances that alcohol dependent people may well be suffering from. So why don't we look at our final case now and this one's a little bit different isn't it?

This case involves a 33 year old male with chronic alcohol dependence who was admitted to a rehabilitation centre for detoxification. During the first two days of his admission he was stable but on day three he started to develop visual hallucination and was aimlessly wandering with a relevant speech and was refusing all of his medications including his lorazepam and risperidone and was spitting out his tablets. He became increasingly agitated and was physically restrained and he was then found unresponsive and he was found to have hypothermia and an unrecordable blood pressure.

Blood tests showed elevated liver enzymes and a raised anion gas metabolic acidosis. An ECG showed ST depression, sinus tachycardia and right bundle branch block and despite best efforts he could not be resuscitated. A post-mortem examination was undertaken and the internal examination revealed an edematous and congestive brain with patchy subarachnoid hemorrhages over the bilateral frontal lobes. Both lungs were edematous and the heart had multiple TQ hemorrhages over the posterior of both ventricles and there was sub-endocardial hemorrhage present over the left ventricle.

The liver also showed macrophysicular staitosis with an inflammatory infiltrate and fibrosis. Assembles were also taken with toxicology and these were negative and based on the post-mortem findings, the histopathological findings, the negative toxicology and the circumstances, the cause of death was attributed to complications of delirium, trellons, secondary to acute alcohol withdrawal. So why don't we unpack this a little bit? When people regularly use alcohol, their brains get used to it.

Yep, so chronic alcohol consumption can cause downregulation of GABA pathways. Alcohol basically activates GABA and tolerance develops so large amounts of alcohol are needed for this inhibitory effect. It can also then lead to upregulation of excitatory glutamate to counteract the inhibitory effect of alcohol. And so when alcohol consumption is abruptly stopped, excitatory signaling in the form of increased glutamate continues to stimulate NMDA receptors excessively, particularly neurons in the locus coeruleus leading to the sympathetic nervous system going to overdrive and this leads to the effects seen in delirium trellons.

In essence, you've withdrawn the alcohol, the nervous system is basically going really really hard on the accelerator and you've taken the brakes away. Yeah, exactly.

So cardiac arrhythmia is a known cause of abrupt deterioration in DT patients and multiple theories have been put forward to explain the cardiac effects associated with DT including failure of small intramyocardial arteries to dilate in response to increased oxygen demand, magnesium deficiencies all sought to play a role and the high level of circulating catecholamines, cyclodrenaline, noradrenaline leading to myocardial stunting or directly damaging the heart muscle which can mimic an occlusive coronary event and I think that was the mechanism they thought was most likely in this case.

So delirium trellons can be fatal but can also be treated, IV benzos are the gold standard treatment alongside fluids, electrolyte replacement and thiamine supplementation. And benzos stimulate those GABA receptors once again, don't they, and help allow you to taper down rather than going entirely cold turkey. So let's take a little bit of a step back from these really clinical cases and look a little bit more general then. When people generally think of drug deaths, people are normally thinking acute opioid toxicity or stimulant toxicity or something like that, not really thinking about alcohol in this way.

And it's odd because alcohol, it can kill you acutely, you can drink yourself to death if you drink a very large amount in one go. But more often than not, the deaths associated with alcohol are longer term chronic effects that ultimately come to a conclusion like some of these cases. It essentially dismantles your normal physiology over a period of time. And I guess that's kind of why a lot of people don't consider it to be like a drug of abuse when you're thinking about these sorts of things because the effects and the negative effects are so long term that it's not really on the forefront of people's minds.

No, that's fair. And it is also, despite being the biggest drug killer globally, it is also the most socially acceptable. Yeah, for sure. And they're probably related, right?

Probably there are many more deaths because it's so socially acceptable. I think one of the other things I want to look at in these cases, really highlighted it was in all three of these cases, no alcohol was detected, right? Yeah. And actually, that is a point in itself, obviously, with the acute alcohol withdrawal, that is by definition, alcohol withdrawal, but other metabolic disturbances that can occur in the context of chronic alcohol use, often not always do seem to precipitate in periods of abstinence.

So given how complex a lot of the biochemistry and multifactorial pathology going on in these cases, are we correctly identifying all alcohol deaths? Oh, I'd say probably not. They're so complex. There's always lots of different things going on in each of these cases.

There's many different histopathological findings and other things going on, but I think it must be really hard to identify it. There probably are cases of pancreatitis, for example, which perhaps get put down as pancreatitis. Yeah. I guess in all three of these cases, there was a clear social history of chronic alcohol use.

Yeah. But I guess if you've not got that social history... It's hard to build that full picture. Possibly, yeah.

I think another thing that these cases highlighted, in fact, was there was a coexistence of chronic alcohol use and social isolation, wasn't there? Yeah. In all three of these cases, these were people that lived alone, they needed support, they needed essentially care. Yeah.

And sadly were very isolated. And I guess maybe the two kind of go hand in hand a little bit. I'm not sure what tends to come first. But it is a really sad situation.

I mean, we see so many chronic alcohol deaths in our line of work, don't we? Yes. And often the story is very similar to that, that people are living alone, they're isolated. So I sort of suggested it at the start about what would alcohol be classified as if it was discovered today.

But what do you think? Do you think if we didn't have a social history of alcohol going back thousands of years and it was discovered today... I don't think it would be used nearly as much. And you can kind of see a trend with a lot of young people now who just don't drink.

And they've decided to go sober and use other things... Like ketamine. Like ketamine, rather than alcohol. Because they recognise the harmful long-term effects of it and they don't like how it makes them feel.

So yeah, I think if it was discovered today, it wouldn't be used nearly as widely as it is. Cynical part of me for a moment. Price might also be pushing some of the younger people out of the market. Oh, possibly, yeah.

But as you say, perhaps not necessarily a bad thing, all in all, in terms of long-term. So alcohol is a funny one, isn't it? I certainly enjoy tequila at the weekend. You do.

And I shouldn't, but I quite like it to relax on occasion and it is almost a real conundrum whereby this very socially acceptable chemical that we have on our Friday nights after work or at celebrations is also a chemical that leads to significant harm, mortality. Also these cases show that it isn't perhaps through mechanisms that everybody thinks about. Yes, liver disease and increased cancer risk and so on are much bigger, bigger causes. But actually there are some hidden causes of death and mortality associated with chronic alcohol use.

Well, I hope you've enjoyed listening to us this week. Do give us a like. Give us a follow. Share us with your friends.

Thank you. Have an amazing week. And we'll see you next time. Bye.