Episode 49: Arsenic - A Victorian Poison in the Modern World

Transcript

Hi everyone, welcome back to the Tox Lab. I'm Rebecca. I'm Rob. This week, we're going to be looking at possibly the most iconic of poisons, arsenic, the king of poisons.

And really we're going to be asking a key question, which is how can a poison that's been present on earth since the earth came into existence, that's most famously known for murders in the Victorian period, how is that still relevant to today? Now we've got three very recent papers all looking at arsenic, which we're going to dive in and have a look at. But first, I did want to dive a little bit into the history of arsenic. Before we jump 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, which we're fairly active on over there. So feel free to comment and like our posts. 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 dive a little bit into the history of arsenic.

As I said, at the start, the king of poisons, inheritance powder, it's got all sorts of fun names. They're pretty good names. I thought we could play a little game, actually Rebecca, truth or lie, lie, L-Y-E, toxicology pun. I'm going to ask you some uses of arsenic in the Victorian era.

And you're going to tell me if they're true or not. Okay. So first of all, was arsenic used as a beauty product? Yes, that's true.

It was, yes, indeed. Complexion wafers sold as non-toxic. They weren't non-toxic. Wallpaper.

Oh, I want to say that's a lie. This is true. So wallpaper and book coverings, they made these beautiful green pigments with arsenic copper salts. Okay.

And you still see them occasionally, not so much because recently they realized that there was a lot of old books in old libraries poisoning people. I think the National Trust had to have a clear out, but they really, really, really beautiful color, the pigment, it really is, but highly poisonous. One for you, baking powder. I think that's true.

No, that's actually a lie. Is that a lie? Yeah, even the Victorians weren't that bonkers. Rat poison.

True. True, yeah, that was the, really when people did poison each other, that was probably the most accessible form of arsenic. And finally, medicinal tonic. True.

That is also true. Yeah, that is also true. So arsenic really was this cure-all and poison-all in Victorian times. And because of the fact that particularly arsenic trioxide, white arsenic, the powder that people would poison each other with, because it was so easy to obtain.

And at the time, forensic toxicologists didn't really exist. People were getting away with murder, left, right and center. They did then bring in the arsenic act, which brought to control it. And subsequently, poison laws have all developed and now arsenic's virtually unobtainable.

I did want to, since we're talking about the history of arsenic and we're a toxicology podcast, give a shout out to James Marsh. He was a Victorian chemist who actually developed the Marsh test. And he was partly responsible actually for bringing the arsenic into control, if not through legislation, but through the fact that he was able to prove in court that people had been poisoned with arsenic. So there were two tests originally that people were using for arsenic.

And these tests were very nonspecific and they faded. And one day he was actually in court on an arsenic murder case. And he had done the arsenic test. But by the time the jury was shown the key piece of glassware, the color change that he had demonstrated had faded.

And he did what all good scientists do when they're humiliated in court. He went back to the lab and came up with a better test and he developed the Marsh test. And so you take your biological sample, you add a load of acid and you add zinc and it generates hydrogen. Hydrogen then reacts with arsenic in the sample to form arsenic gas.

And if you run that gas through a heated tube, the arsenic decomposes and you leave the metallic arsenic behind in the glass. And that was the premise of the Marsh test. And he was able to then demonstrate murders quite convincingly involving arsenic, which again led to a decrease in its use as a murder weapon because suddenly it wasn't quite so easy to get away with. He was able to get sub milligram limits of detection as well, which I'm quite impressed with actually.

So why don't we now turn our attention then to modern toxicology and how this poison, because it really has fallen out of use, hasn't it? It's no longer available in hardware stores as rat poison, pretty much controlled everywhere. Industrial processes do occasionally still use arsenic, but very rarely. But it's still an issue.

So the first paper we want to look at is a paper looking at arsenic exposure across the US through drinking water. And this is one crucial quirk of arsenic actually that we're all exposed to it at very low levels. It's present in the soil, it's present in groundwater. What's crucial is how much of it is there.

And this study looks across the US. So in the US, regulated public drinking water is a major source of exposure to inorganic arsenic. And the US Environmental Protection Agency has a maximum contaminant level in the water for arsenic. And that's at 10 micrograms a liter.

It varies across other countries. And I think the Netherlands has maximum contaminant level of like one microgram a liter. And this study wanted to look at whether the level of arsenic in public water affected birth outcomes. As it's known that arsenic present at greater than 50 micrograms a liter is associated with adverse birth outcomes, including preterm birth and low birth weight.

So in this paper, they looked at 13,998 births from 35 different cohort sites and used zip code tabulation area estimates of mean population weighted public water arsenic concentrations. And then they looked at a variety of different outcomes. So preterm birth, which was classed as birth, occurring at less than 37 weeks. A low birth weight, which they stated as being less than 2,500 grams.

Babies that were small for gestational age. And then they looked at a birth weight for gestational age Z score. So out of these nearly 14,000 births, the mean age of the parents was approximately 30.8 years. 56% were white, 12.4% were black, 7.2% were Asian.

And the prenatal public water arsenic concentration ranged from less than 0.35 micrograms per liter to 37.28 micrograms per liter. So for 53% of participants in the study, the prenatal water arsenic concentration was less than 0.35 micrograms per liter. 25% had water arsenic between 0.35 and one microgram a liter. 22% had a water arsenic of greater than one microgram a liter and 1.7 had water arsenic greater than five.

And in this specific cohort, those that had a water arsenic level greater than five micrograms a liter were more likely to have low birth weight infants. So an absolutely massive and ambitious study, wasn't it? It recruited huge numbers of people and essentially correlated arsenic exposure with birth weight. There was a huge amount of variation of arsenic exposure, wasn't there?

And this is one of the issues that arsenic exists in minerals in the ground. And different parts of the world are exposed to different levels of arsenic in their drinking water. And it also accumulates in crops as well. So it can be diet, can be dietary exposure through grains and rice and things like that.

So this study showed huge variation of arsenic exposure across the population and did seem to suggest that even well below the EPA's cutoff, there was an association with lower birth weights. And preterm births as well. And preterm births as well. Now the absolute magnitude was quite small, wasn't it?

I think it was something like 10 gram decrease in birth weight for every microgram increase in exposure. So it really was statistically significant on this scale, whether it's clinically significant on an individual basis is I think a lot harder to unpack. But it does seem to show this public health issue that arsenic is, doesn't it? That it is poisonous, even at very, very low concentrations, much lower than the acute poisoning that we were seeing in Victorian times.

So we do need to be clear about this paper. This is just an association, isn't it? We can't prove causation. No, and they did mention in their limitations that they don't have data as to whether people were drinking tap water or whether they're drinking bottled water, for example.

So yeah, it's quite hard to. Microplastics in the bottled water. The other possibility actually is if this arsenic exposure is coming from groundwater, it's possible there's other heavy metals in there as well, isn't there, lead, manganese, and so on. So it is possible that there are other confounders underlying all this data.

But it does demonstrate a really interesting point and maybe raise an interesting question. Is there ever a safe limit for arsenic on a population level? And actually it has been debated over the years as to whether arsenic is an essential mineral or not. Because there's been a few questionable studies where they tried to take various animals and completely restrict arsenic from their environment and they didn't do so well and recovered when they were given very small amounts of arsenic.

These experiments have basically not been repeatable. There's been so many issues with the data. And the general consensus is that arsenic is not a trace essential mineral. But it is an interesting question.

And this data does suggest that even very, very low levels of exposure, well under what we would call toxic in inverted commas, may have some adverse effects. So that's very low level exposure on a large population. Let's move into now more acute exposure. So we've got a couple of different case reports, haven't we?

Let's look at the first one. Just a quick one before I dive into this case that is mentioned of self-harm in this. So if that's something you don't want to be listening to, feel free to skip or listen to a different episode. So this first case involves a 33 year old female who deliberately ingested 10 grams of elemental arsenic in a cup of coffee in a self-harm attempt.

Within 30 minutes, she developed nausea and self-induced vomiting, which contained black particulates. And she then developed two episodes of dark colored diarrhea. She presented to the emergency department who after consultation with the poison center transferred her to an academic hospital to be treated with dimer caperal. She was then evaluated by the medical toxicology team for 12 hours post-ingestion and was asymptomatic with normal vital signs and a normal physical exam.

She was then given 500 milligrams of succima by mouth every eight hours while waiting for arsenic test results. And succima is the oral version of dimer caperal. She arranged in hospital for four days without evidence of arsenic poisoning. The succima was discontinued after three days and she was transferred to psychiatry before being discharged.

So looking at her test results, 12 hours post-ingestion before the succima was administered, her blood arsenic was found to be a concentration of 113.8 micrograms a liter, a random urine arsenic. A random urine arsenic showed that the inorganic arsenic was present at greater than 5,000 micrograms a liter with organic arsenic being present at less than five micrograms a liter. 36 hours post-ingestion, they repeated this and her blood arsenic was 109 micrograms a liter. And in her follow-up 19 days post-ingestion, her blood arsenic was five micrograms a liter.

Her spot urine showed an inorganic arsenic of 87 micrograms a liter and the organic arsenic in that spot urine was present at 22 micrograms a liter. Someone obtained inorganic arsenic, ate it, went to hospital, recovered and didn't show any signs of arsenic poisoning. No. So the second case involves a 20-year-old female who deliberately ingested elemental arsenic in a self-harm attempt and presented to the emergency department 30 minutes post-ingestion and it transpired that she'd also obtained this elemental arsenic from the same supplier as the individual in case one.

In the emergency department, vital signs and physical exam were all normal. Abdominal radiography showed radio-opaque material in the intestines and the stomach. And after consultation with the poison center, the patient underwent gastric lavage and multiple metal fragments were retrieved. This was followed by a whole bowel irrigation with polyethylene glycol electrolyte lavage solution and an upper endoscopy removed some more fragments.

Whole bowel irrigation was discontinued on day four due to hypokalemia, hypocalcemia, hypernatremia and hyperkalemia, likely due to the high volume of lavage solution. And a colonoscopy was also unsuccessful at removing the remaining radio-opaque fragments. This patient went on to develop a ventilator-associated pneumonia and was extubated on day seven. The remaining intestinal opacity cleared on hospital day 16, but the patient developed no signs of arsenic toxicity and was transferred to inpatient psychiatry.

On day two of their admission, they did do a 24 hour urine arsenic which showed a total arsenic of 459 micrograms a litre. The inorganic arsenic was present at a concentration of 253 micrograms a litre. Methylated arsenic was present at 206 micrograms a litre and there was an undetectable level of organic arsenic. On follow up at day 18, this was repeated again and the total urine arsenic was 104 micrograms a litre and this was exclusively organic.

So second case remarkably similar to the first case. So my understanding is that these were both supplied by a website that was selling periodic table elements so people can collect the elements of the periodic table in a sort of nerdy novelty fashion. And in both cases, the individuals consumed these pieces of arsenic and didn't really get that unwell at all, which is surprising. When you think about how poisonous arsenic was thought to be and indeed is in the Victorian era, what the hell happened here?

I mean, they ate grams of the stuff and it just shows how arsenic and actually a lot of metals, their toxicity is related to what form they're in and the oxidation state. Toxic arsenic exists as two different oxidation states. Arsenic three plus, arsenic five plus, they're the poisonous arsenic. This was elemental arsenic, so arsenic zero, not oxidised and really poorly water soluble, really insoluble.

And so it really just passed through them, didn't it? Without having any real serious harm. And in fact, possibly some of the treatment may have been more harmful than the arsenic itself. They obviously did absorb a bit, didn't they?

Because their concentrations did increase. I wanna break that down a little bit actually because you said some words in there that people may not be quite so familiar with. So when it comes to testing arsenic in samples, blood, urine, whatever, often we measure the total arsenic, which is the, as the name suggests, all of the arsenic in the sample. But arsenic actually exists in a few different forms, doesn't it?

You mentioned organic arsenic and inorganic arsenic. And it's the inorganic arsenic that's poisonous. So arsenic three plus, arsenic five plus, inorganic forms of arsenic. And that is then converted by the body to methyl forms, monomethyl, dimethylarsnics.

And these are species that the body adds methyl groups to to excrete. These are a bit toxic too, even though they're technically organic at this point because they've got that methyl group attached. But often when we think organic arsenic, we're actually talking about arsenic that's bound to betaine. And this is really, really common in fish.

If you eat a tin of tuna or some prawns, your total arsenic will skyrocket very quickly for a very short period of time, 12, 24 hours, and then return to normal. But it's considered completely non-toxic. And so when we look at the arsenic results in this case, there was a bit of a breakdown, wasn't there, between inorganic and organic? Initially the inorganic spiked and then I think there was a little bit of organic in one of them.

And at the end, I think they broke it down further, didn't they? They described the methyl groups separate from organic. Yes, yeah, in case two, they had the methylated arsenic breakdown as well. Speciated as well, yeah.

So I mean, it's a fascinating case. This one really caught my attention because I must admit I was surprised by this when I saw the headline for people consumed arsenic with no apparent ill effects. It's to do with this water solubility and how actually elemental arsenic is relatively safe. Heat up that elemental arsenic and produce arsenic trioxide.

Totally different story. And that was what the Victorians used to poison each other. Rebecca, why don't we now dive into our third paper? So this final case involves a 29-year-old who had been transferred to hospital with abdominal pain, nausea, and vomiting.

They had a history of GERD, IBS, gastroparesis, PTSD, OCD, and generalized anxiety disorder. Seven months earlier, she had developed progressive sensory motor, polyneuropathy, visual decline, bowel and bladder incontinence, skin rash and flaking, and poor oral intake with a 25% weight loss. She'd also been hospitalized previously for stress-induced cardiomyopathy and ventricular tachycardia. Six months prior to this admission, she'd had a blood test which showed elevated AST and ALT levels, which are markers of her powder cellular damage, although not specific.

And on this admission, her temperature was 37 degrees. Blood pressure, 121 over 91. She had a heart rate of 122 beats per minute and a respiration rate of 20 beats per minute. Her physical exam showed jaundice and diffuse abdominal tenderness and bilateral legoedema.

Blood tests showed a low hemoglobin, a raised ALT, AST, gamma GT, ALP, bilirubin, INR, and ammonia, and she rapidly developed ankylopathy. They began to investigate for causes of her liver injury and heavy metal exposure was thought to be a potential cause due to the multi-system symptoms that she had been experiencing, including the ankylopathy, polyneuropathy, anemia, hair loss, et cetera. She'd previously had lab tests completed by a psychiatrist which showed raised antimony levels, but this was never followed up and there were no subsequent treatment for this. Antimony toxicity is not something I've ever come across.

No. An MRI and CT scan showed diffuse hepatic steatosis and a biopsy showed severe and macrovascular steatosis, cannalicular cardiostasis, ductular proliferation, epipathoid portals, sclerosis, and mild parenchyme or iron deposition. They looked at copper as a potential cause for the symptoms, but copper analysis was normal. They completed organic acid analysis which did show a raised urine erotic acid and a low serum citrulline, which could potentially be a sign of OTC deficiency, but whole exome sequencing excluded this.

Urine and serum heavy metal testing was negative, but due to this increased suspicion, hair and nail samples were taken to assess for chronic toxicity, the serum and urine are only useful for assessing acute toxicity. When testing the hair, this showed an elevated level of arsenic at 25.2 micrograms per gram and the nails also showed elevated arsenic present at 6.1 micrograms per gram and this is consistent with chronic arsenic exposure.

They then used ammonia scavenger therapy, which led to an improvement in her liver injury and neurological status and repeat urine and serum arsenic levels were still negative and hair and nail arsenic levels also decreased. Patient presents the hospital with a weird range of symptoms, obvious liver disease, something going on there, but also a lot of these other stranger symptoms, neurological symptoms, things like that. They go heavy metal fishing and identify arsenic as the culprit. Yes, but only in hair and nails, not in blood or urine.

So let's talk about that for a moment. Arsenic really does three things, doesn't it? We've talked about the chronic public health impact with that first paper. Acute toxicity, which we would possibly have expected in our other cases involving elemental arsenic ingestion, but we didn't see, was the classic Victorian short illness and die, profuse GI symptoms and death.

Chronic toxicity is where people are exposed to raised levels of arsenic over a long period of time and that's possibly what we're looking at here. Now arsenic is toxic through a few different mechanisms. AS5 plus can behave a bit like phosphate and get incorporated into cells like phosphate and then it doesn't work like phosphate because it isn't. And the three plus form can actually bind to proteins and inactivate enzymes.

And so the general toxicity picture is this generalized metabolic disturbance. Cells can't do what cells need to do. And over a long period of time, it leads to a lot of chronic health conditions. And in this case, possibly presented as liver disease.

What's crucial here is that blood and urine were both negative, but it was the hair and the nails that demonstrated raised arsenic. And that's because it's cleared from the blood and urine relatively quick. But if you've been exposed to chronically toxic levels over a period of time, you need to look at longer term matrices to actually demonstrate that. So there was convincing evidence of long term arsenic exposure in this patient.

And crucially, we were talking about seafood earlier. Seafood arsenic won't get incorporated into the hair and nails. So it probably wasn't seafood. It probably was inorganic arsenic.

And it was thought to account for all of her symptoms. So the arsenic exposure does explain the hepatic stoetosis either directly or indirectly via rapid extreme weight loss. And the arsenic toxicity also explains the portal fibrosis and the neurological, gastro, dermatological, hematological and cardiac signs and symptoms. And it can also cause encephalopathy, which was seen in this patient.

So it does kind of nicely wrap up the sort of multi-system picture we were seeing in this patient. There's something very unsatisfactory though about this case, at least from my perspective. Where did the arsenic come from? I know, it's really annoying that I don't tell you.

The source was never identified, was it? The patient came from an area that wasn't believed to have high arsenic in the groundwater. They denied deliberate self ingestion. And they also reported that their soil and water were tested independently and no arsenic was found.

So it remains a mystery. The hair and nails did suggest significant exposure. The symptoms could be caused by this exposure. And yet no source was found.

You can see arsenic exposure from dietary sources rather than fish. Rice and other grains can accumulate arsenic. And if you've got a diet that's very heavy in rice, that can push up your arsenic. And potentially to a level that would be considered chronically toxic.

Although chronic toxicity leading to symptoms like this, I think you'd have to eat an awful lot of rice. I think it's more pushes you into the public health risk kind of exposure category rather than the symptomatic toxicity bracket. So I think this case really is a little bit unexplained, isn't it? Where did the arsenic come from?

And was it really the culprit? I guess one of the names. No. So three really, really interesting papers, all very different, all looking at slightly different aspects of arsenic all from this year despite the fact that arsenic's been known about for centuries.

So it does show that even old poisons can still teach us new things. Definitely. Do we need to be thinking about arsenic more as toxicologists? That's a good question.

I mean, it's virtually unheard of in homicidal poisoning these days, isn't it? Particularly at least in the UK and I suspect globally. But I'm thinking more as clinical toxicologists when we've got these complex patients. This third case, I wish I knew where it had come from.

Yeah. For sure. I guess it's something to just keep in the very back of your mind if you are struggling to come up with a reason. Heavy metal fishing.

Yeah. Was it specifically requested? We don't know. Or did they do an elemental screen on the ICP-MS?

I think they screened for lots of heavy metals. Yeah. So they weren't sure exactly. Based on the multi-system presentation, they thought heavy metals were involved but weren't sure what heavy metal was involved.

So I think they did screen for a variety of heavy metals. So we've moved a long way from the marsh test when it comes to testing for arsenic now. We often use what's called ICP-MS, Inductively Coupled Plasma Mass Spectrometry. And you can use this in such a way as to do a broad screen, can't you, for elements that aren't supposed to be there in a biological sample.

And it's really helpful for things like arsenic, lead, uranium, anything that's not supposed to be in a biological will shine like a beacon when you do a broad screen. Well, I do hope you've enjoyed listening to us this week. Talk about how a poison from a couple of hundred years ago is still relevant to toxicologists today. If you've enjoyed listening, do share this episode with your friends, social media.

We'd really appreciate the exposure and thank you all for coming back and listening. We really do appreciate you all being here. Hope you will have an amazing week and we'll see you next time. Bye.