Episode 54: From Nits to Novichok - A Deep Dive into Organophosphates

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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 exploring the surprising link between head lice, farming, and chemical warfare. So we're going to jump in with head lice first.

Rebecca, you ever had lice or fleas? I found head lice, yeah. How did you find it? Annoying, I just remember like the hours spent with my mum and her nit comb trying to pull them all out of my hair as a kid.

Yeah, I've got two young children at home and nothing makes your heart sink more than the email from the school saying, head lice are in the class and you need to check your children. And then when they do get them, they're an absolute nightmare to get rid of. Well, we're going to be looking at a case today of poisoning from head lice treatment. 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 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 our episodes, you can email us at thetoxlab@gmail.com. So Rebecca, why don't we dive into the first case? So this first case involves a seven year old child with no previous medical history who was admitted to the pediatric emergency department following the application of a milky green lotion anti-lice treatment to the scalp by their father.

Approximately one hour after application, the child presented with digestive symptoms including profuse, pale diarrhoea and vomiting with no other clinical signs. Around five hours after the application, the child began to exhibit neurological signs including confusion and loss of consciousness. The patient then developed acute respiratory distress syndrome with labored breathing, bronchial congestion and an SpO2 of 83% requiring oxygen therapy.

The patient was then admitted to the pediatric neurology and clinical exam revealed that patient was normotensive, tachycardic at 144 beats per minute and had a GCS of six with fixed bilateral constricted pupils and was unresponsive to stimuli. Chest x-ray showed thoracic distension and an EEG showed evidence of frontal lobe seizures which were treated with midazolam and levetiracetam. Blood tests revealed an acidosis with a raised PCO2 and a lactate of 4.3 millimoles per liter, leukocytosis, thrombocytosis and a hypokalemia at 2.2 millimoles per liter.

The patient was admitted to the pediatric ICU for intubation, decontamination and monitoring given their worsening respiratory condition. During this time, it was mentioned by the parents that Paris green had been applied instead of anti-lice solution and Paris green is a copper aceto arsenide complex that was used up until the 1940s as a larvicide and can cause GI symptoms such as vomiting or diarrhea. So this is an arsenic containing treatment, right?

Based on this, plasma and urine arsenic were measured using ICP-MS which revealed normal arsenic levels and they also did segmented hair analysis which didn't show any raised arsenic so they could exclude this. And while the neurological and GI symptoms fit with this, the respiratory symptoms did

not fit with this poison. So based on the combination of diarrhea, miosis, coma, and respiratory distress, this supported a diagnosis of a muscarinic syndrome related to exposure to a cholinesterase inhibitor.

And based on this, they sent samples for cholinesterase activity which was measured in whole blood with a result of 313 units per liter which is well below the reference range of 1,900 to 3,800 units per liter. So what's going on here? He's got a reduced cholinesterase activity. What does that actually mean?

Let's break it down. So a very common neurotransmitter in the body is acetylcholine. This includes nerves in the brain, also nerves attached to muscles, really, really common neurotransmitter. And the way that acetylcholine works at these junctions between neurons and neurons and muscles is that acetylcholine is released.

It binds to a receptor, the other side of the neuromuscular junction or the other side of the synapse. And then an enzyme called cholinesterase breaks that acetylcholine down. And that's what balances the signal between activation and then inactivation. Compounds that inhibit the enzyme cholinesterase stop that breakdown.

So acetylcholine is released from the neuron, binds to the receptor. It then isn't broken down and you get this permanent activation. And in this case, he tested the patient's cholinesterase activity, didn't they? And it showed that his enzyme activity was well below that, which was expected.

And this therefore could have been responsible for his clinical syndrome. There's an acronym, isn't there, that tells you the symptoms that you see with cholinesterase inhibition, SLUDGE. There's actually a few different ones, but SLUDGE is probably my favorite and the one that I remember. And so it stands for salivation, lacrimation, so crying, urination, you get bladder incontinence, defecation, bowel incontinence, GI upset, and emesis.

And this was a pattern we were seeing, weren't we? We were seeing initially GI symptoms. And then later symptoms can be things like labored breathing and inability to breathe. And this is because the muscles are essentially activated and they're never depolarized.

They never inactivate. So this antil isolation was brought in by the parents and was tested using GCMS, which revealed the presence of diazinone. And diazinone is an organothiophosphate derivative and is classified as a moderately hazardous pesticide by the WHO. Diazinone was detected in the plasma sample using untargeted high-res mass spec and was present at a concentration of 38 nanograms per millilitre.

They also detected some phase one metabolites, including 2-isopropyl-6-methyl-4-pyrimidinol, two acidic metabolites, diethylphosphate and diethylthiophosphate, and then four metabolites that had previously not been reported in humans. The patient was then started on a treatment of pralidoxime methyl sulfate four days after initial management until the near total disappearance of neurotoxic signs, which occurred approximately eight days after their admission.

The patient was then discharged from the pediatric ICU 13 days after the first admission to hospital that had persistent bronchial congestion, mild balance disorders, generalized hypotonia and peripheral neuropathies. So it was admitted to a specialized pediatric unit for long-term follow-up. This is an interesting case, isn't it? We don't use cholinesterase-inhibiting pesticides as lice treatment in the UK.

Generally, I think there might be one that is still prescribed very occasionally, but in general terms, we use things like mineral oil treatments or silicon-based treatments. I've got to say, they probably are

much less effective than cholinesterase-based treatments. If your plan is, let's get rid of the lice, but clearly there's a risk here of systemic toxicity. And I think it's useful to consider this case actually, because this case occurred in France, I think, didn't it?

But the parents had immigrated from Romania, so even if a compound is banned in one particular country, it doesn't mean you're not going to see presentations from people moving around, which is possibly what had happened in this case. I think this case also shows the power of high-res accurate mass screening, doesn't it? It's the fact that the lab was able to identify this compound and a load of metabolites. It's really quite impressive.

So let's move into now, away from head lice, a more, an agricultural angle. So this next case involves a 23-year-old male who'd ingested approximately 300 mL of 60% 1605 emulsion four hours before he was admitted to hospital. 4A is a widely used insecticide in China, and it's highly toxic. It's volatile and inhalation is the main route of poisoning.

It causes irreversible inhibition of acetylcholine esterase, and it can also cause DNA damage and cytotoxicity. So on arrival, the patient exhibited deliriousness, restlessness, urinary incontinence, sweating, tears, and shortness of breath. His blood pressure was 164 over 112, and he had a heart rate of 132 beats per minute. He was treated with a warm-water gastric lavage, atropine, and IV pralidoxime.

15 minutes later, he experienced violent vomiting, and he became short of breath, and was comatose with an SPO2 of 81%. Blood gas analysis showed a pH of 7.21 with a raised PCO2 and a lactate of 8.7 millimoles per liter. The patient was then intubated and ventilated and transferred to the ICU, where he underwent a hemoperfusion. In the ICU, he had a GCS of coarse breath sounds, slow response to light, and a heart rate of 125 beats per minute.

He was also hypotensive and remained acidotic with a lactate of 10.5 millimoles per liter. They also went on to measure his serum cholinesterase activity, and that was measured at 268 units per liter, which again was well below the reference range. Eight days after the initial admission, the patient experienced psychiatric symptoms, and they hypothesized this was the result of the high dose atropine he was being given. He was then sedated.

His serum cholinesterase activity was regularly measured, but remained low until day 20, when sedatives were then gradually withdrawn. On day 23, his serum cholinesterase activity had increased to 1,634 units per liter, and they stopped the hemoperfusion. On day 27, his serum cholinesterase activity had increased to 3,592 units per liter, and the patient was then stepped down from the ICU. And on day 34, the patient had recovered and was discharged from hospital.

So let's dive into some science a bit more with this second case, then. So they've talked here about some of the treatments used. They were using atropine and they were using pralidoxime. So as I said earlier, cholinesterase inhibiting pesticides stopped the breakdown of acetylcholine, and so these neurons and these neuromuscular junctions get activated and don't get deactivated when they trigger.

There are a few different varieties of acetylcholine receptors, and so their expression is different in different parts of the body. And you have, we've talked about this before actually, haven't we, where we were talking about the mushrooms. You get the muscarinic acetylcholine receptors, and you get the nicotinic acetylcholine receptors. And atropine is a competitive antagonist of the muscarinic acetylcholine receptors.

So as acetylcholine is present at the receptor and it's not being broken down because there's no cholinesterase, atropine can jump in and inactivate that receptor. So it kind of blocks the effect of acetylcholine. It doesn't do it to all acetylcholine receptors. It only does it to a select few.

And these are the muscarinic class. And what that does is it actually speeds up the heart crucially, which is why we're giving it here. One of the roles of acetylcholine is in the parasympathetic nervous system, which leads to the rest and digest response and lowers the heart rate. Atropine jumps in and actually helps raise the heart rate again.

So it's a really, really important treatment in cholinesterase poisoning because it preserves that key cardiac function, which is what you need to live. Crucially though, it can actually be toxic at two high doses. So it is important that if you are giving atropine, it's not just some magic bullet. You do need to make sure you give appropriate doses and titrate clinical effect.

Or in this case, actually, I was really interested. They actually measured the concentrations and did therapeutic drug monitoring of atropine, which is not something I've come across. Now, the other treatment they gave is praladoxime. And oximes are another treatment for cholinesterase inhibitors.

And so the actual chemical effect of these compounds, they're compounds called organophosphates. They're organic compounds with a phosphate group. That phosphate group binds to the serine residue at the active site of cholinesterase. And it forms a covalent bond and stops the enzyme working.

And then this bond undergoes a secondary chemical step and it maybe loses an alcohol group. And at that point, it's completely inactivated. And oximes actually bind the phosphorus in the organophosphate and actually yank it off of the cholinesterase enzyme, but only if they can do it before that secondary loss of an alcohol group occurs. And this we call aging.

At that point, it becomes permanent inactivation and resistance treatment. So crucially, you need to give oximes really early on to try and preserve as much enzyme function as possible. So this was very similar clinically actually to the first one, wasn't it? Although the presentation was clearly very different.

This was deliberate ingestion of a very toxic pesticide. Again, a pesticide that's widely used in China and other parts of the world banned by the EU. So currently not something used routinely in farms. Agricultural exposure to cholinesterase pesticides is quite a big problem globally and particularly poorer income countries do still use a lot of these older pesticides.

And there is quite a lot of either accidental exposure at work or in this case, deliberate exposure. So that's head lice. And we've talked about farming. And we can now see that there is a link between head lice and farming.

I mean, they're both pesticides effectively. How does this relate to banned chemical warfare? So on the 4th of March, 2018, the quiet city of Salisbury in Southern England became the center for mystery that would soon capture the world's attention. That afternoon, Sergei Skripal and his daughter, Yulia, were found unconscious in a park bench in the city center.

Yulia was found foaming at the mouth with her eyes wide open and they were completely white. They were rushed to a hospital where doctors fought to keep them alive, both remained in critical condition for weeks and no one knew what could have caused a sudden collapse. Turned out Sergei wasn't just any local resident. He was a former Russian military intelligence officer who once acted as a double agent for British intelligence.

Investigators then began to suspect that this was no accident, but an assassination attempt. Samples collected from the scene and from the victim's blood was said to porten down where Novichok was identified, a nerve agent belonging to a family of highly toxic organophosphates. Further investigation traced the contamination to the front door handle of the Skripal home and this was the likely point of exposure. Even touching the surface had been enough to deliver a potentially lethal dose.

During the investigation, Detective Sergeant Nick Bailey, one of the first officers to enter the Skripal residence, also fell seriously ill after being exposed to the same substance and he too was admitted to intensive care. And miraculously, all three of them survived and were eventually discharged more to talk after a long and difficult recovery. But the story doesn't end there. On the 30th of June, just a few miles north in the nearby town of Amesbury, tragedy struck again.

A man named Charlie Rowley had found what he thought was a discarded perfume bottle in Salisbury. He then gave it to his partner, Dawn Sturgess, who sprayed the perfume on her wrist and she had collapsed within minutes. Despite intensive treatment, she had died eight days later and it transpired after testing that the perfume bottle had contained another shot. And this was a case that probably shook the world, didn't it?

It shook the UK, certainly. To this day, Russia denied all involvement. Now this case raised quite a few questions afterwards. In terms of, I think, the handling of such a case because obviously, initially, nobody knew what had happened.

Perhaps reasonably, there wasn't any reason to suspect anything. I believe the individuals were treated initially for opioid poisoning. They were found on a bench, a bench that may be associated with people who use drugs. So it was believed that they had suffered an opioid overdose.

And you can see why. They had Pimprick pupils, they were foaming at the mouth. There were some clear signs consistent with opioid toxicity. And yet, actually, it transpired.

It was, in fact, Colin Esteray's inhibition. Crucially, we're looking at a very different class of compounds from the pesticides here, aren't we? These are deliberately engineered agents designed for mass poisoning. Interestingly, Novichok isn't one thing.

Novichok is a class of agents. I believe the rough Russian translation is newcomer. So the newest generation of nerve agents. Okay.

And there was a massive cleanup operation as a result of this. It's quite a difficult chemical to get rid of. I know the screwball home took about four months to decontaminate there to take the roof off and go through bit by bit to try and decontaminate it. Three ambulances and five paramedic cars were destroyed.

There were 16 police vehicles that were also destroyed as a result of this, and they were all buried in the landfill. Absolutely huge amounts of devastation as a result of the contamination. And what's crucial here, really, we're dealing with agents that are, A, incredibly potent. So very, very small doses could be significantly toxic.

And where we were talking earlier about compounds aging, how quickly the enzyme becomes permanently inactivated with these Novichok agents, it's very, very fast, much quicker than some of the cholinesterase inhibiting pesticides. So that window for giving oxime treatment is much, much narrower. And crucially, there's just this environmental persistence. They seem to be really, really hard to decontaminate.

I do think it is somewhat ironic that this happened in Salisbury of all places. It's on the doorstep of Porton Down, which is famously the only lab in the UK that handles compounds like Novichok. And it is bizarre, isn't it, that headlights treatment and Cold War chemical weapon poisoned by exactly the same mechanism. So I think there were some lessons from the Salisbury poisoning.

I think that initial first responder and how it wasn't what it looked like at first glance. So we've explored the spectrum, haven't we, from NHTs to Novichok. What lessons can we learn or should we learn from this? Because I think compounds that inhibit cholinesterase, very, very poisonous, not

something we see often at all.

And yet clearly, as these cases show, very occasionally can end up in a healthcare facility, potentially samples can end up in a lab. It's something to bear in mind, in the back of your mind, could this be a cholinesterase inhibitor? Particularly if you're dealing with an acute presentation of somebody who's poisoned. Yeah, and I think it also highlights the importance of teams working together, because the clinical team will obviously have seen the symptoms in the presentation and communicating that with the wider lab who are doing the testing to make sure that we're covering things we need to cover based on presentation.

I think it's really important. Let's talk quickly about testing, actually, because cholinesterase testing is available. It's probably not available very, very quickly, depending on your local lab's availability, of course. But quite crucial, because that is the bit you can diagnose, isn't it?

If somebody's got reduced cholinesterase enzyme, particularly in these cases where they did measure it, I mean, it was absolutely through the floor compared to the reference population, that's your answer. So that, I think, is kind of a crucial point. And then subsequently or alongside using the mass spec to actually look for cholinesterase inhibiting compounds, if that's a pesticide, possibly that might be relatively easy. If that's a nerve agent, that might be a bit harder.

I don't know how many people are routinely screening for those. And I've got no sense of concentrations. I mean, we know these things are incredibly potent. It's entirely possible you need a really, really good mass spec to pick them up.

These cases certainly have left me thinking about cholinesterase inhibitors moving forward. In parts of the world where organophosphate pesticides are used, they're going to be cases. People see the cases. I think actually where we might need to keep our eye open is where people do move and bring things like the hair treatment around the world.

I've certainly been involved in a case. It wasn't a cholinesterase pesticide, but I've been involved in a case where somebody had brought in a pesticide outside of the country. And it was only with a good bit of work on the mass spec were we actually able to identify it and work out what had happened. So these things do happen.

Chemicals do move around the world, even if they are banned in your jurisdiction. Well, I hope you've enjoyed joining us this week as we explore the surprising link between headlights, farming, and Cold War chemical weapons. Do give us a like, give us a follow, share with your friends. As always, we really appreciate you all being here and listening.

Hope you all have an amazing week and we'll see you next time. Bye.