The Tox Lab

Episode Transcript

The Codeine Controversy

Pharmacogenomics, breastfeeding, morphine exposure and the problem of influential edge-case toxicology.

Edited transcript
Timestamps removed. Obvious automated transcription errors have been corrected for readability while preserving the conversational style.

Clean Transcript

Hi everyone, welcome back to the Tox Lab, I'm Rebecca. I'm Rob. This week we are going to be looking at what is perhaps one of the most impactful and yet controversial cases in forensic toxicology. So Rebecca, what are your top five most impactful cases that have really influenced you and don't say ones that you've written up and published?

Fair, okay. I mean, Shipman is one that comes to mind. Absolutely. Yeah, that's definitely in my top five. I mean, the one that we haven't covered on the podcast, I definitely wanted it at some point is that poisoning involving poison dart frogs. Okay, interesting. That's just an interesting weird one, it just sticks in my head. Completely fair. Was this a specific case?

Yeah, it made headlines think a couple of months ago, but we definitely need to cover it. Okay, write that one down. I wasn't even aware of a poison dart frog case making headlines. There's been a few hasn't there over, well, certainly in terms of my top five, Shipman is definitely significant. I think there's absolutely loads that have really influenced practice, really had significant impact, but I think really the top one for me, and this is a case that I learned of very early on in my career and has in the last really few years, but particularly in the last few months, even, really started to come under scrutiny as being a case that is really filled with controversy.

That is the 2006 case of the breastfed neonate of which the mother was given codeine and the baby sadly passed away from morphine poisoning. Before we dive into today's episode, if you want to step today with our content, you can find us on Instagram @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 want to get in touch with episodes or comments or ideas, you can email us at thetoxlab@gmail.com. So as I said, this really was an iconic case, and it's definitely a case that's always stuck in my mind.

So Rebecca, why don't you give us the summary of this case? So in April 2005, a full-term, healthy male infant showed intermittent periods of difficulty breastfeeding and was lethargic. This started when he was seven days old. He'd regained his birth weight by 11 days of age, but on day 12 he appeared grey and his milk intake had fallen, and he was sadly found dead on day 13. The mother was being prescribed a preparation of 30 milligrams of codeine and 500 milligrams of paracetamol that for episiotomy pain, at two tablets every 12 hours which was reduced to half of this on day 2, but continued for two weeks.

A post-mortem examination showed no anatomical abnormalities, and blood was taken from toxicology and morphine was detected at 17 ng/mL, but typical neonatal serum concentrations of morphine from mothers who were taking codeine and breastfeeding their children range from 0.2 to 2 ng/mL. The mother had stored milk on day 10, and this was also tested and had a morphine concentration of 87 ng/mL, and a typical range within breast milk after repeated maternal codeine at 60 milligrams every six hours was equated at 1.9 to 20.5 ng/mL.

Genotyping was also completed for the cytochrome P450 enzyme CYP2D6, which is the enzyme responsible for catalysing the O-demethylation of codeine to morphine, and the mother was classed as an ultra-rapid metaboliser. The maternal grandfather, the father, and the infant had two functional

CYP2D6 alleles classified as extensive metabolisers. They determined that the clinical and laboratory picture was consistent with opioid toxicity leading to neonatal death. So we've got a few things here to unpack, haven't we?

As I say, this case really was a case that really opened up my eyes to the idea of pharmacogenomics and how different genotypes can affect how people metabolise drugs differently. So let's dive into the pharmacology a little bit, just so we understand we're all on the same page. codeine is a relatively weak opioid. It is converted to morphine by CYP2D6, and it is the morphine that has the principal opioid effect of codeine. CYP2D6 is quite polymorphic. People have varying degrees of activity of CYP2D6. Most people exist somewhere in the middle and convert a typical amount of codeine to morphine.

Some people don't metabolise codeine at all, and they actually, on average, tend to be what we call codeine non-responders. They actually report very little analgesic effect from codeine. On the other hand, the other end of the spectrum, you get people who are ultra-rapid metabolisers, people who convert more codeine to morphine. And in this case, then mum was an ultra-rapid metaboliser. And some other facts about this case also deserve a little bit of unpacking, so the baby's morphine concentration was very high. Yeah. Certainly a lot higher than typically seen in babies who are exposed to morphine from breast milk from people taking codeine.

And so the hypothesis was in this case, then, wasn't it, that the mum's genotype, ultra-rapid metaboliser status, she converted more codeine to morphine, and that then led to an increase in exposure of morphine to the baby, and baby, sadly, passed away. And I think mum did suffer some symptoms, didn't she?

She was started on an initial dose of codeine, and that was actually reduced because she was feeling opioid-like effects. Yeah. Consistent with her ultra-rapid metaboliser phenotype. Now, this paper had a huge impact. Yeah. It influenced codeine prescription. Yeah. The advice was suddenly don't give codeine to lactating women because of the risk. It created a whole research group that looked at the safety of drugs in pregnant women, newborns and infants. And there really was an absolutely huge impact on the world of drug prescribing and toxicology.

And it also led to mothers after delivery of C-section being prescribed stronger opioids like hydromorphone or oxycodone, which then put them at greater risk of persistent opioid use and addiction. So they're quite serious consequences from this paper. Absolutely. So codeine is generally considered a relatively weak opioid, and you're right. Actually, this did push some people to be prescribed much stronger opioids due to the belief that codeine may have been unsafe in some of these people. So what happened next?

Why is this case so controversial? Well, the reason we're talking about this now is actually as of the third of Feb this year, the Lancet, which originally published this paper, has actually issued an expression of concern regarding some of the data and methodological concerns regarding what was actually published at the time. Now, even prior to this retraction notice, this case has been subject to quite serious debate. There have been quite a few editorials and comments published looking at this data and really asking questions about whether the conclusions drawn in this paper really were

supported by the data.

So there was a short comment published in the Lancet in 2008 in response to this paper, which did have some thoughts. The assessment of post-mortem redistribution of drugs hasn't been studied in neonates, so there was a question as to whether that morphine level was actually as high as it was when it was measured post-mortem or whether that level was the result of post-mortem redistribution. There was also a point raised that there might have been post-mortem hydrolysis of glucuronides, which could have increased the concentration of free morphine, therefore pushing it up to make it look like it was a concentration higher than it was.

And that is another very valid point actually in post-mortem work. I have seen cases with a high total morphine. You reanalyse the free morphine a month later. You get a different number because those glucuronides are not stable in the post-mortem interval. And beta-glucuronidase, which is present in breast milk, can hydrolyze morphine glucuronides, therefore increasing the free morphine and that was a comment that was brought up in this 2008 comment. Okay, so the breast milk itself could contain higher concentrations of free morphine because glucuronides may pass into the breast milk.

And essentially the conclusion from this 2008 comment was that we can conclude that the baby has absorbed some morphine, but we don't really know how much morphine. I think that's completely fair. I think that is one fact in this whole debate that is really not up for debate. Yeah. That there clearly was morphine present in this child. The question really was how did it get there and why was the level so high?

And this case was subject to another criticism, wasn't it? Another paper came along a little while later, which again looked at some of these. And actually the author actually sought to really reanalyse this case as much as possible and went back to the early data as much as they could. So as the paper published in 2020 titled "The Implausibility of Neonatal Opioid Toxicity from Breastfeeding" and sought to reanalyse this case and brought up lots of problems with the original article. So in the original case, the ultra rapid metaboliser phenotype of the mother and the high morphine concentration of breast milk that was frozen three years before death led them to conclude that the child died from opioid toxicity due to enhanced maternal conversion of codeine to morphine and the passage of a larger amount of morphine into the breast milk and this led to the FDA warning against the use of codeine and breastfeeding mothers.

The amount of drug ingested via breast milk is represented by the relative infant dose, which is an estimate of the daily dose ingested by an infant expressed as percentage of the weight adjusted maternal dose. So relative infant dose of 100% means that the infant received the same dose per kilogram as the mother, but for morphine this is between 2.5 and 7.5% and for codeine this is between 0.3 and 1.2%. So in other words, if you work out the dose that the mother's been exposed to when you look then at the dose and infant will receive through breastfeeding, we're looking at between two and a half to seven and a half percent of the total dose.

Yeah, for morphine. And less for codeine. So the morphine concentration, as mentioned in the original paper, is completely discordant with breastfeeding neonates, who typically have morphine concentrations ranging from detectable to 2.29 ng/mL when mothers are taking 60 milligrams of

codeine every four to six hours. The codeine concentration in the neonate, which was not originally reported in the article, was found at a concentration of 300 micrograms per litre, which is approximately 50 times higher than the peak concentration that would have been expected from mothers taking codeine while breastfeeding.

And let's unpack this codeine concentration a little bit. This is where things start to get weird. Because a codeine concentration of 300 micrograms per litre or 0.3 milligrams per litre, sort of ballpark therapeutic, high therapeutic, really, for people taking therapeutic doses of codeine. And by that, I'm talking 60 mg every four hours. So that is not an unsubstantial codeine concentration. And the morphine concentration detected in breast milk seems to be far too low to account for the morphine concentration present in the neonate.

So a concentration in breast milk of 87 ng/mL, which is found in this case. If the baby had consumed 1,000 mL of breast milk, which is unlikely given the observation of poor feeding, the resulting dose of morphine would have been 87 micrograms, but suggested dose of morphine for a four-kilogram infant is up to 3,800 micrograms per day. And that wouldn't account for the morphine concentration that we've seen in this case. So when you actually calculate the morphine exposure based on the breast milk concentration, there's no way the baby would have got that morphine concentration from the breast milk alone.

So the conclusion from this 2020 article was that neonatal opioid toxicity from maternal codeine use during breastfeeding could only arise from a highly improbable combination of factors, including a high maternal codeine dose and unusually high concentrations of opioids in breast milk, large volume of neonatal intake and profoundly impaired clearance. There is an alternative hypothesis, of course, and it really doesn't bear thinking about, but it does seem to be in context the most logical conclusion and that is codeine ingestion.

Yeah. And so you can see why this case has become suddenly very controversial. There is now an expression of concern on that original article. The Lancet hasn't officially retracted it yet, but certainly there are concerns regarding some of the strength of the conclusions being too strong. And there were also variations of this article, I believe, by the same authors in a couple of Canadian journals that have since been retracted. Yeah, so I believe the original authors actually had quite a few articles retracted. Although this particular one, I think the question here is not so much whether the methodology is flawed, but rather whether the conclusions were perhaps, in retrospect, too strong.

And I guess it must be quite challenging as an author when you have come to this conclusion, although it might have been too strong, where you are worried that if you don't say something that maternal codeine use could be having quite a serious catastrophic impact on infants, you're going to want to kind of raise the alarm whether that should have happened or whether more research should have been done before that happened is up for debate, but I can sort of sympathise with them. I think that's a really, really fair point.

I think you're absolutely right. A way of viewing this is an observation was made, a conclusion was made that actually perhaps this drug we thought was safe may not be safe. Do we need to implement some sort of action to avoid any further harm?

And I think that that is a completely fair point. I think some of the questions arise, for example, why wasn't that codeine concentration reported in that first paper? Because that may have led to other authors, even if the initial author didn't consider that part of the conclusion. It may have at least then led to others to challenge the view sooner. I do think this is really, really tricky, because I think first, we're looking at this with the power of nearly 20 years of hindsight. Yeah. And our understanding and our knowledge of pharmacogenomics, our understanding of codeine, our understanding of post-mortem toxicology, it's grown so much over these last few years.

So I do think that we are looking at this now with the power of hindsight. And I think the other sort of point here really is that although there are concerns regarding this case, edge case toxicology does exist. Yeah. We know that there are weird cases that every so often don't seem to fit the mould of our understanding. And so it isn't necessarily wrong to identify a really unusual edge case. In fact, we often feel like we need to publish the edge cases. But I think what's challenging here with this one is just the impact it had.

As you said, the effect it had on codeine labelling and prescribing and then how that may have led to other more potent opioids actually being used, which may actually have been less safe in retrospect. The other possibility here actually is that perhaps people may have declined pain relief, perhaps suffered unnecessary pain for not wanting to cause harm to their child, which I completely appreciate. So what are the lessons learned from this case?

I think one lesson is the importance of providing all your data, like codeine concentration that wasn't in the original article might have influenced a reviewer to ask a couple more questions and then maybe it would have been phrased differently so the FDA wouldn't have given their prescribing advice, for example. So I think the twist here was that I don't think there was ever any ill intention to hide that codeine. There is an interview with one of the authors of that rebuttal paper from 2020 and the individual gives an account of actually going back to the original draft and apparently the original article submitted to the Lancet in draft was actually 12 pages long and included the codeine, the paracetamol concentration, and the Lancet actually wanted to shorten it to a single page and so key details got cut.

I do think that you're right though, I think had it been published, even if the article had been published in that state, it may have led to other professionals in the field to at least debate it. And I think that is key here. We never know all the information. As scientists, we take information and draw conclusions and that's what we do. That's what we do day in and day out. And sometimes those conclusions are supported by the evidence at the time and subsequently turn out to be wrong and that's okay and that's the debate that we really need to encourage.

Yeah. And that's why we always say if you're listening to the Tox Lab and you disagree with us, do get in touch because we would love to hear from you. And I think that it really shows that we need more of that. Yeah, polite, professional, academic debate and maybe had we had that in this case, perhaps some of these outcomes may have been different. That is very true. Scientific debate is how we move forward in all fields and how we gain knowledge and look at new ideas and things from a different perspective. We are all human at the end of the day and we have our preconceived notions on things and without that debate and those conversations, you'd be looking through a very narrow lens on a lot

of things.

No, you're absolutely right. You're absolutely right. Well, I hope you've enjoyed following along with us this week as we look at one of the most iconic and yet controversial cases in forensic toxicology history. We haven't really touched much on that New Yorker article but we'll put a link in because it is well worth a read. There is a lot of really good storytelling in there about this case. And as always, if you've got thoughts or feelings on this case, do get in touch or leave a comment. We'd really like to hear from you.

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