Episode 63: Bupropion Toxicity - Mechanisms of Cardiac Conduction Abnormalities

Transcript

Hi everyone, welcome back to the Tox Lab. I'm Rebecca. I'm Rob. This week, we're going to be talking about a rather strange drug. Rebecca, I want you to name for me a drug, which is an antidepressant, a giving up smoking aid, and can also be crushed up and snorted and has been called poor man's cocaine.

See, I didn't know that one. Is the drug you're thinking of bupropion? It is. We're going to be taking a look this week at bupropion.

And actually, we've had two requests recently to talk about bupropion, one looking at seizures and one actually looking at management of cardiac toxicity. So we're going to be taking a bit of a deep dive into what goes on in the context of bupropion overdose and also how some of these cardiac manifestations come to be. 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'll also have a page on LinkedIn and a fairly active one there.

And for those of you who don't need social media but want to get in touch with episode suggestions, like the ones we've had today, or comments about episodes, you can email us at thetoxlab@gmail.com. So what is bupropion? Bupropion is often thought of as an antidepressant drug and it sees a lot of use in the US as an antidepressant. Interestingly, in the UK, it's not licensed as an antidepressant.

It is licensed as a smoking aid or rather a quitting smoking aid. And it is a very, very interesting compound. It has a long, rich history and although crushing up and snorting it and referring to it as poor man's cocaine is not common, it's also got that side to it as well. So just want to start a little bit on the history.

First developed in the sixties. And at that time, antidepressants really came in two main categories, tricyclic antidepressants, which were known to be potentially quite toxic, had quite narrow therapeutic windows. And we were also using monoamine oxidase inhibitors and they can be quite tricky to use as well. You've got to have dietary restrictions if you use them, because certain food stuffs can cause side effects.

And in general, monoamine oxidase inhibitors have fallen out of favor in clinical use. And so Bupropion was born as this novel compound, structurally completely unrelated to other antidepressants. It's actually closer to cathinones and amphetamine stimulants in terms of its structure. And in the eighties, there was a big launch, but there was a problem.

And the problem was that it caused seizures. And at launch, this was quite notable. There were quite a lot of reports of seizures for people starting on this drug. And so it actually had its license withdrawn quite quickly.

Later in the eighties, it was resurrected and it was then trialed again, this time at a much lower dose. So the initial trials, the initial launch were at higher doses. But there was also a lot more guidance on titrating a dose and also strict contraindications. And really from the eighties onwards, it saw use as an

antidepressant.

And in the nineties, a slightly odd side effect was observed in that people who were prescribed Bupropion were actually smoking less. Oh. As a result, it saw a second life as an aid to quit smoking. Oh, that's very interesting.

And then into the two thousands, various modified release versions were produced. And this actually helped with the seizures to a degree because people's blood concentrations were a bit more stable. They weren't getting huge peaks and troughs. And so now it's a really common antidepressant.

It's generally considered to be quite an effective antidepressant, particularly amongst individuals that have got sort of a lower energy depression as opposed to an anxiety-driven depression. But it is also a drug that is not uncommonly encountered in the context of overdose and toxicity. And that's where we're going to be focusing today. So Rebecca, why don't we dive in at our first paper?

So this first paper is a case study involving a 16-year-old female who was brought to the emergency department following an out-of-hospital cardiac arrest. She had a history of major depressive disorder and suspected bipolar affective disorder and was being treated with 300 milligrams of lithium, 150 milligrams of bupropion, and 20 milligrams of fluoxetine daily. Earlier in the day, she reported generalized discomfort and stayed home from school. And by midday, she had become increasingly agitated and developed progressive altered consciousness.

She eventually collapsed with generalized limb stiffness, which was misinterpreted by her mother as a temper tantrum rather than a medical event. A few hours later, the patient became cyanotic and unresponsive and displayed persistent limb rigidity and an ambulance was called. When the ambulance arrived, she was found seizing, laying face down with perioral cyanosis and continuous convulsions. They repositioned her and found her to be pulseless before CPR was started.

Return of spontaneous circulation was achieved after 21 minutes of CPR and the patient was transported to the hospital with adrenaline being administered and an endotracheal intubation was performed in the emergency room. When she arrived to the ED, she was hypotensive with blood pressure of 85 over 50 and she was also tachycardic at 110 beats per minute. She was comatose with a GCS of three and her pupils were bilaterally dilated and fixed. Blood test revealed a severe metabolic acidosis and she was hyperglycemic and had a raised white cell count and she was given IV sodium bicarbonate to correct the acidosis.

An ECG was performed which showed a new right bundle branch block with a prolonged QRS interval of 132 milliseconds and a prolonged QT interval. A urine toxicology screen was also performed and this was positive for benzodiazepines, which they report as being consistent with her prescribed meds and she was admitted to the PICU. Yeah, I saw this line in this paper and I'm not sure I understand which benzos were on her prescribed meds because there weren't any. Yeah, it confused me too.

I don't know whether she was given a benzodiazepine because she was seizing and they've just not stated that and assumed that we know what they're talking about, but I don't know. It wouldn't be an unreasonable medical treatment to have given in the context, would it? A review of the patient's medication showed that approximately a month's supply of bupropion was missing and this was equal to 4,200 milligrams or 90.3 milligrams per kilogram, and the family estimated that the ingestion had occurred approximately six to seven hours before the cardiac arrest.

Serum analysis, six hours post-ingestion revealed a concentration of bupropium of 3,200 nanograms per millilitre and the therapeutic range is typically between 150 and 250 nanograms per millilitre. The progressive agitation that the patient had experienced in the morning might have been a pre-dromal phase that had been described in severe bupropium toxicity cases previously and this occurs during

early neurological excitation before a tonic chronic seizure occurs and this delayed timing of the collapse is consistent with an overdose of slow-release bupropium. So this is something you see, isn't it, with extended release and slow-release drugs.

It's possible for somebody to take a very, very large overdose and for symptoms to get progressively worse over a period of hours and that sounds like what happened here, doesn't it? There was a degree of anxiety and agitation and then muscle rigidity followed by overt seizures. During the stay in hospital, the patient developed rhabdomyolysis with a CK peaking at 36,636 units per liter on the second day despite an initially normal CK. Following her pediatric ICU admission, the patient received 1,000 milligrams of IV levetiracetam every 12 hours to control the seizures and IV fluids were given to treat the rhabdo.

As the patient recovered, she became agitated and was prescribed quetiapine before bed and lorazepam every six hours. A brain MRI confirmed hypoxic encephalopathy and subsequently manifested parkinsonism with bradykinesia, rigidity, and resting tremor and agraphia, which is the inability to write. An awake EEG showed excessive slow waves suggesting mild to moderate diffuse cortical dysfunction, cognitive assessments revealed impairment in short-term and working memory, calculation difficulties, and left-sided visuospatial deficits, which are all consistent with a hypoxic brain injury.

She received extensive rehab and hyperbaric oxygen therapy but was left with some disability, including diminished attention capacity, reduced digital dexterity, and difficulty completing time-limited tasks. She required continued rehab for her neurocognitive symptoms. So quite a sad case, really, and not entirely uncommon amongst people who suffer from severe depression and other mental health conditions. What actually went on in terms of toxicity?

We talked a bit about the prodromal excitatory phase, and then there were seizures, and then we started talking about cardiac symptoms. So bupropion is a noradrenaline dopamine reuptake inhibitor, but it's actually relatively weak compared to drugs like cocaine. And crucially, unlike a lot of antidepressants, I mean, this person was also prescribed fluoxetine as well, wasn't she? Fluoxetine is a classic SSRI, selective serotonin reuptake inhibitor.

Bupropion's got no serotonin activity whatsoever. It's purely through dopamine and noradrenaline. And so it has mild stimulant effects, and that's the rationale behind people crushing it and snorting it as poor man's cocaine. So it does have a degree of misuse potential.

So at therapeutic doses, it gives this brain an activating profile, a little bit more dopamine, a little bit more noradrenaline, a little bit more energy, a little bit more motivation. And that's really the rationale for why it can work as an antidepressant. But a higher dose is bupropion can cause seizures, which we saw in this case. And so the increase of noradrenaline from bupropion stimulates the alpha-1 adrenergic receptors, and it's this excitation that leads to heightened arousal and reduces the seizure threshold leading to seizures.

Doses of immediate-release bupropion exceeding 450 milligrams can lead to a 10-volt increase in the incidence of seizures. But sustained-release tablets do reduce this risk, and the risk of seizures in patients on doses between 50 and 300 milligrams of slow-release bupropion is similar to that of the generalized population and other individuals on other SSRIs. So we've got two slightly different things here, haven't we? We've got, on the one hand, this increase in seizure risk in people who are prescribed it therapeutically.

And this is well-recognized. Actually, the absolute risk for most people who don't have underlying seizure disorder or underlying other risk factors that may lead to seizures, such as alcohol withdrawal

and anorexia nervosa, actually, the absolute seizure risk is relatively low. Most patients who are prescribed bupropion won't have a seizure, but it will reveal seizures in a handful of patients. On the other hand, in the context of overdose, where a large dose is taken, seizures are quite commonly seen as a symptom, and it's all the same effect, just a spectrum.

And so we've explained seizures, and actually the seizures go and explain some of the other symptoms and signs that we saw, don't they? The raised CK due to muscle rigidity, prolonged seizing, can lead to that. Raised lactate and acidosis, again, coming from prolonged seizure, likely. What was going on with the heart, the cardiac toxicity?

So she did have that initial out-of-hospital cardiac arrest, and did have a 21-minute downtime before they successfully managed to resuscitate her. And then upon arrival to hospital, she did have this widened QRS interval and this prolonged QT interval as well. So let's drill a little bit into widened QRS intervals. And I'm going to have to put my hand up and say, I am not a cardiologist.

So ECGs are not my thing, but widened QRS intervals are a relatively common sign in antidepressant overdose, aren't they? Yeah. Particularly drugs like tricyclic antidepressants, but pupropion has also been implicated in this widened QRS complex. So the QRS interval is essentially the time that it takes for an excitatory impulse to propagate through the ventricles of the heart, and it's part of what is seen on an ECG.

So let me just check I've got this right in my head, because it's been a while since I've thought about cardiac conductivity. So every heartbeat and electrical wave travels through the heart and tells it to squeeze in a neat and organized way. But normally that happens relatively fast and you get this nice organized squeeze from the bottom through the ventricles. In a widened QRS complex, that electrical signal is traveling slower and the nice spike you see on an ECG graph is wider, hence widened QRS.

And so as a result, the heart squeeze is either a bit weak or messy or disorganized. So we're gonna look a bit at possible mechanisms for why pupropion has these cardiac effects in a little bit. But first, we thought we'd have a look at what is a really common treatment in cardiac disease, particularly widened QRS complexes in the context of antidepressant overdose, and that is sodium bicarb. And in this case, the patient was given sodium bicarb.

So Rebecca, why don't you dive into this paper? So sodium bicarb is given as a treatment for QRS prolongation. And in the context of, for example, tricyclic antidepressant overdoses, these act on the HNAV 1.5 channel in the heart which is the sodium channel, and this is blocked by these drugs and can lead to a prolongation of the QRS interval. So when we were thinking about delayed signal transduction through nerves and muscles of the heart, without turning this into a massive cellular physiology lecture, electrical signals travel through cells by the movement of ions, including sodium and potassium.

And tricyclic antidepressants are sodium channel blockers, and they block that sodium channel. And sodium channel blockers, therefore, will slow and reduce that depolarization because they prevent the movement of sodium ions. So sodium bicarb can treat this in a number of ways. One is by increasing the availability of sodium, which can help to out-compete the drug at this channel.

Another way is through alkalinization, which can shift weak bases, which are most sodium channel blocker drugs, to an uncharged forms, therefore they can't bind the sodium channel as well, and that allows them to recover from an activation faster. So this paper is a retrospective clinical study to evaluate the effect of sodium bicarbonate on QRS duration in bupropion overdoses, assess for a dose-response relationship, and describe changes in QTC interval, metabolic parameters, and hemodynamics.

So this is a US study using the research patient data registry query tool, and this is a centralized clinical data registry that obtains data from various electronic medical records and billing systems of 10 hospitals in Massachusetts, including urban, academic, and community hospitals. They performed three queries using this tool, which identified patients over the age of 17 with documented administration of IV sodium bicarbonate during hospital encounter between January 2010 and June 2022. And then they queried this for patients whose reasons for visit was drug overdose within the same encounter.

They then led to ICD-10 codes from the same encounter, and then the encounters where a discharge summary included phrases such as bupropion overdose and its brand names. Duplicates were removed and patients were included if an ECG showed a QRS duration of greater than 100 milliseconds and a repeat ECG was done within four hours of sodium bicarbonate being given. So 182 unique patients were available for chart review, with 37 patients having a documented bupropion overdose, and 13 patients were included in the final analysis. And the median age was 32 years, and 54% of the patients were male.

In all 12 patients where the formulation of bupropion was documented, they were all exposed to extended release formulations. Eight had documented exposure doses, and the median of this was 2,250 milligrams. It's important to note nine patients did have documented co-ingestions, and one was diagnosed with pulmonary embolism on presentation. When looking at effects, six patients developed seizures, one developed ventricular dysrhythmia and cardiac arrest, and four were treated with vasopressors.

One patient did receive 3% hypersonic saline between ECGs, but this did not decrease the QRS duration. So the median pre-sodium bicarb QRS duration in QTC were 116 milliseconds and 495 milliseconds respectively, so these are prolonged. And the median change in QRS duration from the pre-sodium bicarb ECG to the first ECG after initial administration was minus two milliseconds, which was not deemed to be statistically significant, or indeed clinically significant. So let's break down what they actually did.

So they did a retrospective review of patients that had come in with bupropion overdose. They then filtered it down to find all those who had had an ECG treatment with sodium bicarb and then a repeat ECG to see whether that repeat ECG had improved their QRS complex. So despite sodium bicarb being conventional treatment for widened QRS complex in the context of more general antidepressant overdose, doesn't seem to work for bupropion. Is that the takeaway?

Yeah, if you've stayed with us the whole time, you're possibly seeing where we're going with this. And that is that bupropion appears not to act like a classic tricyclic antidepressant. And indeed, why should it? Because it isn't a tricyclic antidepressant.

But I think there has been temptation to lump it in with antidepressant overdoses in terms of management, because it vaguely resembled what was a picture that was seen with tricyclic overdose. Our final paper is looking at possible mechanisms for why bupropion can cause this cardiac effect, but not apparently through a mechanism that's responsive to sodium bicarbonate. So as we've talked about, the QRS interval is the time taken for an excitatory impulse to propagate through the ventricles. And the speed of this conduction is somewhat determined by the resistance of the intracellular connections formed by gap junctions between cardiac cells.

These gap junctions are formed of proteins known as connexin proteins, and bupropion has been linked with inhibiting connexins leading to this QRS prolongation. HCX43, or connexin 43, is an isoform that is the predominant protein in human ventricular cardiomyocyte gap junctions. As the authors of this paper wanted to investigate the ability of drugs to inhibit the connexin proteins using a

parachute-type HCX43 di-transfer assay. So they weren't just looking at bupropion, they were looking at a variety of other drugs and drugs that are also in development.

And this assay works by having donor cells that are loaded with a dye that express this connexin 43, dispersed above a monolayer of acceptor cells that also express connexin 43, and these cells parachute onto the acceptor cells. When the donor cells and the acceptor cells form gap junctions, dye will spread into the layer of acceptor cells and the extent of the spread of dye represents the amount of gap junction coupling between the cells. So as I mentioned, they test a variety of drugs associated with the QRS prolongation that we're seeing that aren't class one antiarrhythmics, and this included bupropion.

And the general finding was that bupropion did not show any connexin 43 uncoupling activity, so basically it wasn't acting by inhibiting this connexin 43 mechanism. In other models, bupropion has been shown to reduce the gap intercellular communication in cardiac tissue, but this doesn't seem to occur via the direct inhibition of this connexin 43 protein, so it might be that it's acting on gap junctions, but not necessarily by this direct mechanism, by something else, and we're just a little bit in the dark as to what that is currently. Interesting, so let's just break this down a little bit because you've used a lot of words there.

Gap junctions are connections between cells, and this is important in the context of a heart, so when an electrical signal stimulates one cell, not only does the electrical impulse travel along the cell, but it will also spread that impulse via these gap junctions to nearby cells. And so in the context of a widened QRS complex where the signal is taking longer to get through the heart, a proposed mechanism is some interference between these connections between cardiac cells. This study set out to try and identify that by, if I've understood this right, attaching donor cells and receptor cells and seeing whether dye travels between them.

Yes, which isn't the perfect model for looking at this because obviously how well dye transfers isn't necessarily the best representation of how electrical impulses are gonna be moving through cells and through those gap junctions to other cells. But effectively they made this model whereby dye transfers exposed the cells to bupropion and it didn't alter that dye transfer. Yeah, they did also look at that HNAF 1.5 channel, which that cardiac sodium channel that we talked about earlier and bupropion was found to not be active at that channel.

So again, that kind of confirms our theory that the QRS prolongation isn't through that sodium channel pathway, but again, isn't directly involved through that connection 43 direct inhibition that this paper was proposing. So to summarize what we've discussed so far, bupropion is a very commonly prescribed antidepressant, works similar to stimulant drugs. It has been associated with seizures, both therapeutic use by lowering that seizure threshold, but also in overdose, it can cause seizures, but crucially also it can affect the heart.

Clinically it resembles tricyclic antidepressant overdose, at least at first glance when a patient presents, but actually sodium bicarbonate, which is a well-recognized treatment for tricyclic overdose, doesn't seem to have the same treatment effects. And this we believe is because it isn't acting through sodium channels, but possibly through gap junctions, although exact mechanism currently not confirmed. So if we go back to that original case then, I mean, that was a really messy clinical presentation, wasn't it?

There was a lot going on out of hospital arrest, followed by resuscitation, profound acidosis as a result of possibly cardiac downtime, but also prolonged seizures. She was treated with sodium bicarbonate, probably we think it wouldn't have made much of a difference on our QRS complex, although she also was acidotic. Yeah, and that can widen your QRS interval. So it might've had some effect, but they

don't go into detail and repeat ECGs and whether that was fully corrected with the sodium bicarb treatment or not.

So that is a mystery. I think this really shows the difference, doesn't it, between the sort of theoretical, let's pick apart this part of this, let's look at this little aspect of this, versus the clinical reality of a patient comes in, the ambulance are there, they've just got to do what they do, they need their protocols, they need guidance on what is the most effective treatment most of the time. And I've got nothing but respect for first responders that go and make those decisions and go and do those treatments because it must be incredibly challenging, actually.

Well, I hope you've enjoyed listening to us this week and thank you again to both the people that got in touch and asked us to talk about bupropium. It's definitely given me quite a lot to think about because I often don't try and get my head too far in the zone about treatments and how treatments work, particularly more general medical treatments in the context of some of these things. So it's actually been really good for me to explore that. If anybody listening has got any other thoughts or any other cases or mechanisms they'd like us to explore, please do get in touch.

Hope you have an amazing week and we'll see you next time, bye.