Episode 47: Clozapine - Unpacking the Complexities of a Unique Antipsychotic

Transcript

Hi everyone, welcome back to the Tox Lab. I'm Rebecca. I'm Rob. This week we're going to be taking a look at clozapine, which has a reputation for being one of the most feared drugs in a psychiatrist's arsenal. Would you agree, Rebecca? Yeah, I'd say so. Big shout out to Casey, who over on Instagram suggested that we cover clozapine on the podcast, and a big thank you. If any of you out there have any episode suggestions and want to get in contact, you can find us on Instagram at @the_tox_lab. You can also message us over on LinkedIn because we're fairly active on there as well, and for those of you who don't use social media but still want to get in touch, you can email us at thetoxlab@gmail.com. So let's dive right in. Clozapine: what is it and why is it so scary to psychiatrists? Clozapine is an antipsychotic drug. It's used to treat schizophrenia, but crucially it's what's known as an atypical antipsychotic and it's used to treat schizophrenia when all other treatments have failed, so it becomes this second-line treatment. It was actually first discovered in 1958 and in the 1970s it was marketed as a miracle new antipsychotic, and then overnight it got withdrawn from the market because there were a significant number of patients who developed what's called agranulocytosis. So one particular type of white cell that's used to fight infection, neutrophils, can be reduced by clozapine in some patients, and there was a cluster of deaths in Finland. So overnight this new miracle drug for treating schizophrenia suddenly had a tarnished reputation. In the 1980s it was actually reintroduced under strict conditions, and in this situation they established a mandatory register of patients who were on this drug and implemented very strict blood count monitoring to ensure that their neutrophil count was not too low and that they weren't at risk of developing fatal infection. In the 1990s more and more evidence emerged showing just how good this drug was at preventing some of the causes of death that we see in people who have schizophrenia, and often that's suicide. But then we also started to see some of the longer-term side effects of being on this drug, and that's really where this reputation for being a scary drug came from. It is both brilliant at what it does and yet at the same time does so many off-target things that there can be quite a few negative consequences of actually being on it. So how does it work? Well, it's a really complicated drug with a lot of modes of action. We're still learning lots about schizophrenia and psychosis, particularly the biochemical abnormalities that occur in these conditions. Most antipsychotics work by blocking one of the dopamine receptors, the D2 receptor. Clozapine does that a little bit, but it also has a load of off-target effects. It blocks certain serotonin receptor subtypes, it blocks acetylcholine receptor subtypes, it blocks histamine, and it's got a really messy receptor profile that just seems to do exactly what is needed to help this complex disease that is treatment-resistant schizophrenia. But at the same time this really wide profile of action leads to some really quite significant off-target effects. But there really is no other drug quite like it, is there, in terms of actually managing this treatment-resistant schizophrenia? So this week we're going to be looking at some effects of clozapine, both acute effects in acute toxicity and some chronic effects through long-term use of clozapine, and also we're going to be diving a little bit into some more recent work looking at how certain drug combinations can further increase the cardiac risk that comes with being on this drug. So Rebecca, why don't you dive into our first paper looking at acute toxicity? So this first paper is a retrospective review of clozapine-related toxicity presentations to a medical toxicology inpatient and consultation service between 2011 and 2021 in Western Sydney, Australia. During this time period 61 patients were found and these presentations were split into

deliberate self-poisonings in which 28 patients presented, accidental overdose in which 20 patients presented, and 13 presented with adverse drug reactions. So starting with deliberate self-poisonings in this category, the mean age of individuals was 40, 17 were male, 11 were female, and the mean dose of clozapine that they'd taken was 3103 milligrams. So to put that into context, most patients will take somewhere between 300 to 600 milligrams a day, sometimes as much as 900 milligrams a day. So these were quite a bit higher than a typical daily dose, weren't they? Yeah. Nineteen of these individuals were on clozapine as a single agent. Nine individuals had co-ingested other meds such as diazepam and olanzapine. Twenty-five of them were admitted under a toxicology service and three were discharged from ED after observation, and the mean length of stay for these patients was about 5.4 days. Some of these patients, about nine of them, were not regular clozapine users. I don't believe they were prescribed clozapine, and the mean dose that they had taken in this group was 2,680, so a little bit lower than the total cohort for deliberate self-poisonings. So a third of these presentations were deliberate self-harm, but actually not by people prescribed clozapine, people deliberately self-harming on other people's clozapine. Yeah. And nine of these patients represented to the emergency department within six months of their original admission and five of these had another instance of a clozapine deliberate self-poisoning episode. Signs in this cohort included drowsiness in 86% of individuals, tachycardia, delirium and hypersalivation. Symptom onset occurred approximately four and a half hours after ingestion and this was similar in regular users of clozapine and in those individuals who were not regular users of clozapine.

Hypersalivation is an interesting symptom seen with clozapine, both in acute toxicity and with regular use as well. It blocks most of what they call the muscarinic acetylcholine receptors, apart from the M4 subtype where it actually activates that, and that's what leads to this hypersalivation.

So moving on to adverse drug reactions, 13 patients presented within this period with a mean age of 41 years, eight males and five females. Nine patients were on other medications including sodium valproate. Other common medications included mirtazapine, escitalopram and haloperidol, and the primary indication for individuals being on clozapine was schizophrenia. The mean daily dose in this cohort was 384 milligrams and the average length of hospital stay as a result of that adverse drug reaction was 5.6 days, with the longest being 21 days. So these were people taking therapeutic doses, yeah, and still having clinical effects related to toxicity.

So five patients experienced chest pains and myocarditis, three had fevers, two experienced CNS symptoms such as drowsiness and seizures, rhabdo was present in two patients and one patient experienced neuroleptic malignant syndrome. Those with central nervous system complications had the longest length of stay and the highest mean dose around 575 milligrams and those who had CNS complications and the neuroleptic malignant syndrome had been on clozapine for over two years before presenting.

As a result of these instances seven individuals had dose alterations which included either drug cessation, dose reduction or withholding of their clozapine. So the final 20 patients included in this paper presented as a result of therapeutic misadventure, accidental ingestion or iatrogenic administration and the mean age in this group was 44 years. Eleven individuals were admitted whereas 9 were consulted and discharged from the emergency department, and the mean length of stay was a lot shorter at two days.

There was also some co-ingestion in this group so two individuals were taking lithium, one was taking sodium valproate, one was taking aripiprazole and one was taking amisulpride. And the most common effects seen in this group were central nervous system-related, which affected 17 of the patients, and that included drowsiness. Myocarditis was seen in three patients. So they categorised patients into three categories: those who had deliberately taken way more clozapine than they were prescribed,

and in those cases they took quite significant doses beyond a daily dose.

But then we've got this group of patients who despite no alteration to their dosing or schedule still presented with similar signs and symptoms and then the third group were accidental cases, broadly similar really to the second group right? Yeah. And it just shows how messy, if we focus on the therapeutic group for a second, it shows just how messy this drug can be right. Some of these patients had been on clozapine for a significant length of time and then suddenly developed toxicity requiring dose changes and that is one of the challenges that psychiatrists face when using this drug therapeutically.

And so not only do you get lots of off-target effects such as the hypersalivation, you also have this really really complex metabolism profile whereby suddenly out of nowhere your metabolism of this drug can change and you can go from therapeutic to toxic fairly quickly. And so why is the metabolism so complex? Well clozapine's broken down in the liver by a few different enzymes, different CYP enzymes 1A2, 3A4 and 2D6, and anything that can change these enzymes can have an effect on clozapine metabolism.

Crucially also some of its metabolites, particularly norclozapine, have some activity as well so there is this complex balance between the parent drug concentration and the metabolite concentration. And there are a few things that can particularly alter CYP1A2. So caffeine, or big caffeine intake, can actually increase your clozapine concentration. Similarly, if you've got a regular coffee habit and then you quit it, it can do the opposite.

Other drugs can do it too, including drugs that are quite commonly prescribed alongside clozapine such as sodium valproate. Infections can do it, so the cytokines released from an infectious process can actually suppress CYP1A2 and you may suddenly then spike clozapine, and this could be really really tricky to manage because you've got a patient who's acutely unwell who then suddenly starts to suffer signs and symptoms of clozapine toxicity. Some of those symptoms such as sedation may actually overlap a little bit with being acutely unwell, and the big one actually is smoking, but it isn't the nicotine that can lead to alterations in CYP1A2.

And believe it or not it's actually the smoke in smoking and wired into our bodies we've actually got a set of polyaromatic hydrocarbon sensors. This is known as the aryl hydrocarbon receptor and I'm not sure I entirely understand why humans and mammals have actually evolved this response to smoke to lead to enzyme induction. It is a bit weird. But it does and so smokers who are prescribed clozapine typically need a higher dose of clozapine because their metabolism is increased by the smoke.

Of course what is happening particularly in this day and age we're seeing increasingly people move from smoking to vaping and nicotine pouches. Suddenly overnight the hydrocarbon stimulation of this pathway is gone. It's not the nicotine they haven't quit smoking as far as they know all they've done is move on to vaping. But from a clozapine metabolism perspective their metabolism for clozapine can slow right down very quickly and again they can develop this toxic syndrome as a result of having too much clozapine.

Why don't we then look at some of the chronic effects of the paper looking at chronic toxicities relating to clozapine use. So this paper is a case study involving a 61 year old female who was diagnosed with paranoid schizophrenia and had presented to A&E following a non-mechanical fall and slow onset confusion. It transpired that she was standing and then fell and had experienced dizziness but didn't have any symptoms beforehand such as palpitations like headiness or weakness and she was prescribed clozapine and so to evaporate for her epileptic seizures.

Over the last six months she had been experiencing multiple unprovoked falls and had eight A&E visits which included many blood tests and CT scans which were all normal. She had developed action tremors and new onset overflow urinary incontinence and her sister had reported that she had withdrawn from her general activities during this time. She'd also experienced a general decline in her mobility and her appetite and her GP reported that she had developed a short gait in tendency to lean to her left while walking and on her latest admission she'd experienced another fall and needed an NG tube to support her feeding.

After consultation with the mental health team they recommended measurement of serum clozapine which was then found to be present at a level of 1,627 micrograms per liter which is three times the upper therapeutic limit. To treat this the following two doses of clozapine were admitted over the next 24 hours and her clozapine dosage was titrated down and repeated measurement was found to be within the therapy range. Subsequently she was tapered off her clozapine as she exhibited no signs of paranoid schizophrenia on a subtherapy dose.

After clozapine was stopped her mobility and cognition improved she regained her appetite and her NG tube was removed. So this really shows how someone can go from being stable or over a period of time developing more and more symptoms associated with toxicity. In this case leading to falls and general withdrawal from from life. There could be quite a lot of overlap as well can't there between side effects of clozapine and toxic effects of clozapine.

To quickly look at some of the side effects sedation was a big thing that was reported a lot of the toxic effects but actually that can be present during normal therapeutic use as well and that can also contribute to weight gain a lot of patients gain quite a lot of weight because they're moving a lot less you can then see increases in metabolic syndrome, diabetes and complications associated with that. Dizziness, low blood pressure often reported. Hyper salivation we mentioned earlier but again that can be an effect.

One very significant side effect and can be magnified in states of toxicity is constipation and actual gut paralysis and this can lead to fecal impaction and bowel obstruction and actually this can be fatal this has been fatal in quite a few cases and so there is a symptom that people on clozapine do need to be aware of and should they suffer from constipation take it very seriously and it could also lead to seizures and as we said at the start in the early trials of clozapine back in the 70s agranulocytosis this reduction in white cell count and increased risk of infection I mean that's pretty much a whole bingo card of all possible side effects of all drugs right it's so broad so unbelievably broad and in toxic states in cases where clozapine levels have crept up because of these alterations in metabolism these side effects can become more and more pronounced and become toxic effects it really is a spectrum isn't it between side effects and off-target effects and then the toxicity symptom yeah one big one we haven't touched on is cardiac toxicity increases in cardiac risk myocarditis and cardiomyopathy both of which come alongside use of clozapine and we're going to look at a third paper aren't we that's going to be looking a little bit at some of the mechanisms of that so as Rob mentioned clozapine can cause some major cardiotoxic effects and risk factors for this can include faster titration onto a drug and being administered other drugs along sides that just only evaporate and this is an uncommon combination as we've seen in the other two papers several of the patients in both sets of papers were also on sodium evaporate as well as clozapine in isolated cell lines and isolated mitochondria high concentrations of clozapine have been shown to impair mitochondrial function through depolarizing mitochondrial membranes and impairing the consumption of oxygen which overall impairs ATP synthesis which can then impact both systolic and diastolic function in the heart leading to cardiomyopathy so that's kind of the proposed mechanism for that's toxic effects so this particular study aimed to determine the acute effects of clozapine and evaporate exposure alone and in

combination on the mitochondrial function of excised human cardiac tissue because most of this research has been done on isolated mitochondria or animal cell line models and things like that so 24 samples of right atrial appendage tissue from individuals undergoing a routine coronary artery bypass surgery were collected these patients were overwhelmingly male with an average age of 67 and a BMI of approximately 27.9 on average among half the individuals have been diagnosed with type 2 diabetes and none of the patients have described clozapine or evaporate in the past so this study was looking at both oxidative phosphorylation and leak respiration using complex one complex two and a combination of the two of the electron transport system after drug incubation and then monitoring the consumption of oxygen so before i jump in leak respiration is the consumption of oxygen by mitochondria caused by a proton leak in the mitochondrial membrane so this can release energy in the form of heat without contributing to ATP production and can also alter the proton motive force used in oxidative phosphorylation so they took some heart cells they incubated them with the different drugs they measured the oxygen consumption and by altering the environment that these cells were kept in you can stress test each individual mitochondrial pathway yeah essentially so when these samples were exposed to clozapine only this didn't affect leak respiration but it did reduce respiration by approximately 34 percent on average in the oxidative phosphorylation assays compared to the control this was when they were looking at complex one complex two and a combination of the two as well there was no significant change in the estimated complex one or complex two linked net oxidative phosphorylation efficiency and we'll come on to that a little bit later when these cells were exposed to evaporate this also caused a decrease in oxygen consumption of approximately 25 percent during complex one and complex two oxidative phosphorylation and a decrease of 31 percent during complex two oxidative phosphorylation compared to the control when these two were combined the mean o2 consumption decreased by approximately 25 percent during complex one and two oxidative phosphorylation and 34 percent during complex two linked oxidative phosphorylation compared to the control which considering you've got two different drugs that have been shown to decrease oxygen consumption i was expecting there to be more of like a cumulative effect and that doesn't seem to be the case in this particular model at least so in conclusion the clozapine decreased the o2 consumption during oxidative phosphorylation through both complex one and two linked respiration and this was to a similar extent that had been seen previously in animal models of cardiomyopathy however in this study it didn't significantly affect the net oxidative phosphorylation efficiency through either pathway suggesting that while clozapine impairs oxidative phosphorylation it doesn't affect like mitochondrial coupling and previous studies have suggested that clozapine can uncouple mitochondria and induce a sort of leak respiration inhibiting oxidative phosphorylation and therefore decreasing the net oxidative phosphorylation efficiency but it's important to mention that a lot of these other studies were using cell lines or isolated mitochondria they were using much higher doses of clozapine whereas the study was using actual human cardiac mitochondria within cardiac tissue itself so there are some differences there which could account for the differences in effect so they did suggest that these results could indicate that clozapine can directly inhibit either complex one and complex two or other upstream enzymes involved in NADH and FADH generation which will therefore inhibit o2 consumption during oxidative phosphorylation you can tell you've got a raw biochemistry background i know there was a lot of raw biochemistry there so they looked at different respiration pathways in mitochondria yeah the conclusion was clozapine affects them yes and in doing so this can lead to the cardiomyopathy what was the effect of the valpro8 it did the same thing but didn't add to it it seems that yeah that's interesting isn't it because it's not uncommon that valpro8 and clozapine are prescribed together we saw that a lot in the case report and the first set of data so there is this mechanism we think this direct effect or indirect effect we're not quite sure on mitochondria and cardiac tissue in particular and this is translated clinically to an increased cardiac risk and recognize cardiac changes with long-term use of clozapine so clozapine a drug with a lot of actions and also a lot

of side actions a lot of side effects a lot of toxicity risk a lot of complex factors that can lead to alterations in metabolism most drugs with this sort of side effect profile would never make it through safety trials why do we need the drug like this i mean treating treatment resistant schizophrenia is hard so if you've got something that works it's the proper balance between like that positive and its side effects and in some patients the benefits outweigh the risks 100 yeah absolutely schizophrenia is truly devastating psychiatric condition we've not really talked much about what it is but clinically individuals suffer from hallucinations delusions disordered thinking but it completely derails normal life and makes living in regular society hard for some people and when we say hallucinations it's not just hearing voices right it becomes complete loss of trust in reality itself as i say it really is devastating and as a result people can't hold down jobs relationships and on average people with schizophrenia die 15 20 years younger usually through suicide or untreated medical conditions because they withdraw from society things like that so it really is an awful illness and if the only tool you've got to treat it is clozapine despite the side effects the benefits far outweigh those risks and it really has been proven to work hasn't it these documented reductions in suicide risk improvements in people's states of mind and well-being people actually able to live a life they couldn't previously live as it really is a an incredible drug at the same time as being this terrifying drug that carries with all of these side effects so going back to the case report the second one they took her off clozapine yeah and she showed no signs of schizophrenia that's unusual it's weird most people who are diagnosed with schizophrenia this is a diagnosis for life and it does make you wonder whether the diagnosis was ever correct in the first place it is a little bit worrying isn't it yeah for sure it's definitely unusual that's not to say i think cases haven't resolved but yeah that that is definitely unusual so what does the future hold well there's lots of ongoing research into new antipsychotics and clearly the holy grail is a drug as good as clozapine or better without the side effects and currently we're not there yet which is why clozapine is still used there has been some drugs that have been proposed some of them do have fewer side effects but actually they're just not quite as good there's some experiments looking at trying to use antioxidant drugs alongside to try and reduce some of that cardiac risk this experimental research is ongoing who knows whether it will be successful and clozapine analogues things like that really are just experimental at the moment but who knows you know there could well be breakthroughs in the future so really to summarize clozapine is a truly messy drug but at the same time it's messy receptor profile really is what makes it do what it does in a way that other drugs don't so there really is no alternative for some of these patients i do want to have a little bit of a take home with regards to the metabolism because i think that's somewhere where if you're listening to this and you're a general practitioner and you've got a patient in front of you who is on clozapine be aware of the fact that clozapine concentrations can change quite quickly in response to alterations in metabolism particularly that smoking one we're always encouraging people to give up smoking because smoking is bad just keep that in the back of your mind i've definitely encountered toxicology cases where an individual had quit smoking been to their gp and instead of the gp recognizing the effect on their clozapine metabolism patted them on the back and said well done for quitting smoking you've done a good thing and sadly that individual passed away a week later from clozapine toxicity i think we're going to wrap it up here i hope you've enjoyed listening this week do give us a like give us a follow share us across social media we'd really appreciate that and thank you all for listening we really do appreciate you all being here hope you all have an amazing week and we'll see you next time bye