Intro

MC: Hello and welcome back. We hope you enjoyed the last few episodes that featured our Memorial School of Pharmacy students. I certainly learned a lot while helping them prepare and record the segments. This month, Cathy and I are getting back in rhythm for this episode on the notorious QT prolongation warnings.

Background and History

CB: Alright Mike, let's start with some background. A standard electrocardiogram or ECG tracing will show waves and they're named P, QRS complex and T waves. They represent the electrical activity of the heart. By looking at it over time, we can see how long it takes different parts of the heart to essentially generate an electrical signal and rest before the next one. From the QRS to T waves, we're specifically observing the ventricles in action.

MC: Right, so the QT interval is the duration of the ventricle's electrical activity. A normal QT is around 420 ms and is quit variable between people. But if this becomes longer, it increases the chance that the ventricle gets an earlier electrical signal. And typically, if it exceeds 500 ms, it can be very, very bad.

In the late 1990s, more reports started coming out about drugs causing prolonged QT and the often fatal consequence of torsades de pointes, a form of arrhythmia where the ventricle beats quickly and abnormally. This led to some international recommendations of what to do about drugs that exhibited the potential to prolong QT during clinical trials.
(Shah, 2002; Darpo, 2010)

CB: The term torsades de pointes for listeners who don't know French, like myself, was coined back in 1966, by French physician Francois Dessertenne, and roughly translates to twisting of the points. Now, I can't read an ECG, but I imagine those waves twisting, turning and being all erratic. I wonder if he had known what an important thing it would become in drug development and research, he would have named it after himself!
(Dessertenne, 1966)

MC: In the English world, maybe we'd come to learn these as Dessertenne waves, which despite how dangerous they are, sounds more palatable. Anyways, we digress. It wasn't until 2005 that an international consensus was struck on a plan to require drug manufacturers to specifically evaluate whether new drugs would prolong QT. This document was adopted by the FDA in the US as well as Health Canada in Canada.
(FDA guidance 2005; Health Canada guidance)

CB: Essentially, drug manufacturers would have to conduct clinical trials with healthy individuals and see if taking the medication would lead to QT prolongation. You get about 100 volunteers to take the drug at various doses and you do ECGs before and after. If there's no change in the ECG, then great! If the drug causes an increase of 5-10 ms or more, then you're going to need another study. If it increases by 20 ms, there would be a stop to any further clinical trials or development. Any effect of the drug would be reported, from no effect to whether it prolonged QT by a little or by a lot.

MC: And for better or worse, all of this information is now populated into product labels or monographs. I say better or worse, because it's great that information is there, but also, this leads to minor effects that are often inconsequential being placed into the pamphlets and handouts that we might give to patients to read.

CB: And from a pharmacist and physician or nurse perspective, our automated drug interaction andadverse effect notification systems will start to warn us about them. Again, that's all good from a safety perspective, but seeing these notifications for a quarter or more of the medications you prescribe or counsel on a day to day basis can be tiresome. Think about your smart phones or tablets and imagine getting a notification every 5 or 10 minutes that requires you to click or tap before it goes away. It's information overload or fatigue. And soon, you may start to ignore most of them and just click it. Or even turn it off completely.

Now I'm probably exaggerating a little, it's not like health professionals completely ignore and don't think about these warnings. Of course we consider them! And here lies the second problem. Prolonged QT is a contextual issue. Let's talk about the individual risks or reasons when QT prolongation or torsades de pointes might be worrisome. There are a lot of risk factors but we'll highlight the common ones.

Risk factors

MC: There are basically about 8 risk factors to consider.
(Al-Khatib, 2003; Trinkley, 2013; Tisdale, 2016; Grindrod, 2019)

Number 1: Female sex

CB: Well of course, us females seem to always draw the short straw!

MC: We've known that there were ECG differences between sexes for over a hundred years, the physiological or biomedical reason for it hasn't been fully uncovered. What we do know is the end point—that in general, females have a longer baseline QT interval, about 20 ms longer. We also know that these differences are not present at birth and it might be something that occurs later, during or after puberty. So it could be hormonal too, for example, a decrease in males with no change for females OR a lengthening for females. Perhaps it is this baseline difference that makes it more likely for females to have torsades de pointes compared to males. Either way, it's important to take this into consideration when it comes to medications.
(Makkar, 1993; Salama, 2014)

Number 2: Older age

CB: And this next risk factor shouldn't be a surprise. The number 2 risk factor is older age! There are a number of reasons why we need to be concerned about age when it comes to QT prolongation. Aside from the fact that elderly patients tend to have more medical conditions and use more medications, physiologically, their ECGs also differ. Like we discussed for females, the QT interval is also longer in the elderly. Reasons for this are mostly unknown. Perhaps it's the aging heart muscle or changes in the autonomic nervous system that ultimately affect electrical conduction. But overall, this means that older age means higher risk.
(Rabkin, 2015)

Number 3: Heart rate

MC: And number 3, is heart rate. QT intervals are often corrected based on heart rate, which is why we see it written as QTc. This is because heart rate inversely affects QT—the slower the heart

rate, the longer the QT interval. And this makes intuitive sense because everything speeds up when the rate is faster and everything slows down when the heart beats slower. So using a mathematical correction to normalize the rate to 60 bpm is a common practice. For our patients, that means a slow heart rate or bradycardia may put them at risk of QT prolongation.

Number 4: Electrolyte disturbances

CB: Risk factor number is electrolyte disturbances. Our cells depend on a delicate balance of electrolytes to function and usually our bodies do a great job of keeping everything operational. When the balance is thrown off it can negatively affect the electrical conduction in the heart. In some medical conditions or situations where you might get electrolyte disturbances such as hypokalemia (low potassium) or hypomagnesemia, the changes to electrical conduction can be problematic. We have to watch out for certain medications that can cause electrolyte disturbances such as diuretics like furosemide, or lithium for bipolar disorder.

Number 5: Previous cardiovascular events and current heart problems

MC: The next one, number 5, is if patients have previous cardiovascular events or current heart problems. And this goes without saying. If someone has had a prior heart attack, stroke, or has heart failure or has significant cardiovascular disease, their risk is also higher.

But what about the common condition, atrial fibrillation? Atrial fibrillation is the fast and erratic beating of the atrium and has its own set of cardiovascular risks. There must be some relationship there as we talked about heart rate being a factor. I thought the same and looking into it, it seems like a longer QT may be associated with atrial fibrillation, but the precise relationships are still being studied. Two of the difficulties are, the variability of electrical conduction in these conditions at different points in time and the patient's life, and the fact that we use ECGs to make these diagnoses, which can also change depending on the situation. What's more important are the medications used, as antiarrhythmics, some of which can prolong QT and intentionally so. And that leads into the next risk.
(Patel, 2018; Roberts, 2017)

Number 6: Using multiple QT prolonging drugs

CB: The next risk is having more than 1 QT prolonging drug onboard. And this is where pharmacists really play a big role. If you've ever looked at the list of drugs that can cause QT prolongation, it would scare you. Last I checked, the list has over 150 medications. Aside from the obvious antiarrhythmics, some of the most common culprits are certain antidepressants, antibiotics and antipsychotics and there really isn't a commonality between these classes of medications. This makes it sometimes hard to predict if something will cause a problem or not. We also know that the dose of the medication can be a factor, with generally higher doses causing more problems. For example, the antiemetic ondansetron used at higher than standard doses can cause prolonged QT. That's not to say that everyone will have this problem, because some people are on 5 or 6 of these without any QT prolongation. But either way, if you're using more than one of these medications together, it is something to think about.

Number 7: Drug interactions with QT prolonging drugs

MC: And number 7, are drugs that interfere with other drugs and here is where it gets complicated. What if you're on one medication that increases your risk for QT prolongation but you need to use another one that interacts with the first one? Or worse, inadvertently use another one that has an interaction? This is something that pharmacists are always on the lookout for and despite

the computer warnings, a big part of our daily decision making. The main problem is when one drug increases the blood levels of another, such as through a drug absorption or elimination effect. Like we mentioned before, the dose of medication is important, so when something like this happens, we have to think about how much more the body will see of the medication, and more importantly, whether it will get to the amounts necessary to prolong QT. If anything, these are the more difficult effects to find because they can also be variable and depending on the patient, sometimes inevitable. But we'll talk about this a little more in a second. For now, we go to the last risk we'll discuss.

Number 8: Genetic predisposition

CB: The last risk is number 8 and that's genetic predisposition. This is the one thing that we really can't control. We're entering this age of genetic testing where you can send a small sample to a company and get pages of results back. These results purport to tell you all your health risks, drug sensitivities, capability of metabolizing drugs, and important for us today, your genetic profile and whether you have congenital long-QT syndrome.

In Newfoundland and Labrador, our population is small and for many years, rather isolated, so rare genetic disorders can be more common. It's called the founder effect, when people in an area are descendants of a small number of people. Some have been identified, like arrhythmogenic right ventricular cardiomyopathy or ARVC, which made headlines years ago because it led to young people getting heart attacks. Luckily, congenital long QT does not seem to be more prevalent in our province. Nationally, about 1 in 2500 people have genetic mutations that are associated with long QT. It may seem like a lot of people, but don't worry, most of the time there are no problems and you wouldn't even notice it. For many medications, it also won't be a problem. However, there are some that should be avoided if you have congenital long QT, such as the common allergy medication, diphenhydramine (Benadryl) or common antimicrobials, like ciprofloxacin.
(Merner, 2008; GEC-KO)

Patient Assessment and Next Steps

MC: So what do we do with all this information? Remember when we talked about the 100 or so people taking the drug in a QT clinical trial? Well, think about when this medication goes out to millions of people, some of whom have congenital long QT or have the risk factors we talked about. What do we do then? And what do we do, when over 200 medications are known to potentially cause this problem?

CB: In an ideal world, we could just avoid all of these medications, but some of these medications are life-saving and necessary for many people. The answer?

MC: It boils down to an individual patient, their individual risk, and the absolute need for a pharmacist's assessment. However, we're not alone in figuring this out. There are some tools we'll share on our webpage that can help categorize and assess patient risk, such as one out of Purdue University. We can also use an online database called CredibleMeds, that gives a risk rating for individual medications. I'll expand on CredibleMeds, because it's super useful and free with an email signup. It can tell you whether a medication is known to prolong QT and cause torsades, whether it is known to prolong QT and possibly cause torsades, whether certain conditions while using the drug cause torsades, and which ones to really avoid in congenital long QT. They also have lists of clinical factors or medical conditions that may be associated with

prolonged QT in medical literature. And yes, there's an app for it too.
(Tisdale, 2016; Grindrod, 2019)

CB: I've used CredibleMeds quite a lot at the clinic. Just a few days ago I had a psychiatrist referral wondering what antipsychotic would be safest in their patient who is also taking and domperidone 40 mg daily. Using CredibleMeds it was determined that olanzapine is the antipsychotic with the lowest risk, being in the conditional risk category whereas other agents like risperidone are in the possible risk category. Olanzapine is the best option, however, we can also work with the physician to decrease risk further by determining if the domperidone is required, if another agent such as a an H2RA could work if treating GERD, and if the combination was necessary we could ask if the dosage of domperidone could be lowered.

MC: No matter where you practice, you're destined to come across issues surrounding QT prolongation for your patients.

CB: Absolutely. Here in Newfoundland and Labrador we are lucky to have the electronic health record. Prior to this, as a community pharmacist who would come across potential QT prolongation warnings during the dispensing process, I felt I wasn't really armed as best as I wanted to be. I didn't know what the patients baseline QT was, if it was measured through a recent ECG at all, I didn't know whether or not the antibiotic that was being prescribed was the only agent possible or if there was another antibiotic that this patient's culture was susceptible to. Now it is a whole new world. In my community practice earlier this week I had a 78 year old lady who presented with a prescription for ciprofloxacin for a urinary tract infection. Upon dispensing the warning came up that the patient was at risk for QT prolongation due to currently taking esomprazole and citalopram. I could easily bring up her health record and determine her QTc. In this case it was 422 ms. Knowing that we could put her above the threshold that we're worried about in females of 460 ms if ciprofloxacin is ordered, I wanted to see if there were other options for treating the UTI. I could view the culture and sensitivity and see that it is also susceptible to sulfatrim and nitrofurantoin. Both are safe, although sulfatrim should be avoided in patients with congenital QT so just to air on the side of caution I contacted the physician to get the prescription changed to nitrofurantoin. I also suggested switching esomeprazole to rabeprazole as it doesn't have the association with QT risk and could be safer if she is to continue on PPI therapy with citalopram. We as pharmacist can certainly play our part with this added access to information!

MC: And this makes me think about when I was practicing in Ontario without access to an electronic health record. I would be dispensing methadone, everyday to the same patients, over and over again, and methadone is known to increase or prolong QT as well, but I had no idea whether it would for the individual patients that came in.

And certain drug classes have multiple agents that cause QT prolongation, but there are usually options. For example, in antidepressants, TCAs have the greatest risk, followed by SSRIs, but there is variation within the SSRI class with paroxetine, fluoxetine and sertraline being safer than citalopram and escitalopram.

CB: And like outlined in the case I mentioned, there are usually other alternatives to antibiotics, just check the culture and sensitivity. If you're not sure if an agent prolongs QT just check with CredibleMeds!

MC: And don't forget to have a look for renal impairment, hepatic impairment, electrolyte disturbances, structural heart disease like heart failure, and also bradycardia as these all play a part in assessing risk.

CB: Always recommend a baseline ECG if a patient is started on a new medication that has the potential to cause QT prolongation if they haven't had one done recently. And the ECG should be assessed on a regular basis.

MC: Question for you Cathy, let's backtrack a little bit. If the normal QT interval is less than <450 but people have a range of values, then if it increases it by 10 ms, is it dangerous for someone who sits around 400 ms?

CB: Well It could be! Conditions change, let's say it is added and only goes up to 410, then they develop hypokalemia from an episode of diarrhea, suddenly they could be at 480 ms. Any prolongation of over 5 ms can be significant, and some drugs causing only a 5-10 ms increase have been withdrawn from the market because of cardiac concerns, making this a common definition of drug-induced QTc prolongation is a 5-10 ms increase. To put it in perspective, sotalol, an antiarrhythmic, can prolong QTc by 30-40 ms and a recent meta-analysis of 16 articles representing all six currently available SSRIs, showed that the SSRIs as a drug class may increase QTc by about 6.1 ms compared with placebo. But citalopram is the worst, being the longest at 10.58 ms. In addition to causing the largest change in QTc interval of all the SSRIs, citalopram has been linked to numerous episodes of torsades de pointes, and dosing limits have been imposed by the FDA.
(Beach, 2014)

Conclusion

MC: That's the answer I was looking for! We hope we've clarified QT prolongation for you and made sense of all the warnings out there. It's something to think about for the many drugs that can cause it and your individual patients on them. That's our time today. If you'd like us to talk about this more or any other topic that you have questions about, send us an email at medthread@mun.ca.

CB: And we'll return next month, with a topic that our new pharmacy resident is interested about. Thanks for listening and stay tuned!

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