Patient Safety Tip of the Week

October 10, 2017 More on Torsade de Pointes

Torsade de pointes is a relatively uncommon cause of sudden unexpected death but one that is potentially preventable (see our June 29, 2010 Patient Safety Tip of the Week "Torsade de Pointes: Are Your Patients At Risk?"). It is a form of ventricular tachycardia, often fatal, in which the QRS complexes become "twisted" (changing in amplitude and morphology) but is best known for its occurrence in patients with **long QT intervals**. Though cases of the long QT interval syndrome (LQTS) may be congenital, many are acquired and due to a variety of drugs that we prescribe. The syndrome is more common in females and many have a genetic predisposition. And there are a number of reasons why this syndrome is more likely to both occur and result in death in hospitalized patients. Hospitalized patients have a whole host of other factors that may help precipitate malignant arrhythmias in vulnerable patients. They tend to have underlying heart disease, electrolyte abnormalities (eg. hypokalemia, hypomagnesemia, hypocalcemia), renal or hepatic impairment, and bradycardia, all of which may be precipitating factors. More importantly they may have the sorts of conditions for which we prescribe the drugs that are primarily responsible for prolonging the QT interval (eg. haloperidol, antiarrhythmic agents, etc.). And many of those drugs are given intravenously and in high doses in the hospital as compared to the outpatient arena. Rapid intravenous infusion of such drugs may be more likely to precipitate Torsade de Pointes than slow infusion.

The drugs most commonly associated with Torsade de Pointes are haloperidol, methadone, thioridazine, amiodarone, quinidine, sotalol, procainamide, erythromycin, azithromycin, the antihistamine terfenadine and certain antifungals. For a full list of drugs that commonly cause prolongation of the QT interval and may lead to Torsade de Pointes, go to the CredibleMeds® website. That site provides frequent updates when new information becomes available about drugs that may prolong the QT interval.

But one matter of real concern is prolongation of the QT interval by **combinations of drugs**.

The FDA (FDA 2016) issued a warning last year about the commonly used anti-diarrheal loperamide (Imodium and numerous OTC formulations) as a possible cause of unexplained cardiac events including QT interval prolongation, Torsade de Pointes or other ventricular arrhythmias, syncope, and cardiac arrest. Apparently, the majority of reported serious heart problems occurred in individuals who were intentionally misusing and abusing high doses of loperamide in attempts to self-treat opioid withdrawal symptoms or to achieve a feeling of euphoria. "In cases of abuse, individuals often use other drugs together with loperamide in attempts to increase its absorption and penetration across the blood-brain barrier, inhibit loperamide metabolism, and enhance its

euphoric effects." The FDA lists the following drugs (noting the list is incomplete) as commonly interacting with loperamide: cimetidine, ranitidine, clarithromycin, erythromycin, gemfibrozil, quinidine, quinine, ritonavir, itraconazole and ketoconazole.

The latter two drugs are antifungal agents in the azole category. Researchers at Duke University School of Medicine recently presented at IDWeek 2017 data about interaction in patients receiving azole antifungals and amiodarone, a commonly used anti-arrhythmic drug (Cook 2017). Senior author PharmD Melissa Johnson presented results of a study of inpatients who were given systemic azoles (fluconazole, voriconazole, posaconazole, itraconazole) and amiodarone concomitantly. Of 252 patients with EKG results there was a mean maximal change in QTc of +32.4ms from baseline from 471.6 ms at baseline (monotherapy) to 504.0 ms (concomitant therapy). The commonly used danger parameter of QTc≥500ms was seen in 25.4% of patients at baseline and a follow-up QTc ≥500ms was seen in 48.8% of patients. Though no cardiac events were apparent in relation to concomitant azole-amiodarone therapy in the study, Dr. Johnson noted that more studies are needed to better understand the safety of azoles given in the context of other QTc prolonging drugs.

Another study (Lorberbaum 2016) used data mining and laboratory investigation to uncover some potential QT interval-prolonging drug-drug interactions (QT-DDIs). They found both direct and indirect signals in the adverse event reports that the combination of ceftriaxone (a cephalosporin antibiotic) and lansoprazole (a proton-pump inhibitor) will prolong the QT interval.

The major risk factors for Torsade de Pointes are potentially modifiable. Since the electrolyte disturbances may be corrected and medications may be switched there is significant opportunity to reduce the risk of torsade de pointes when prolonged QTc intervals are recognized early. But it's pretty clear that it is beyond the capacity of the human brain to remember not only all the individual drugs that may prolong the QT interval but also all the drug-drug combinations that increase the risk. Add to that a general unawareness of the risks for Torsade de Pointes. So we really need to rely upon technology to help us. Clinical decision support systems (CDSS) are the logical answer. We discussed these in our Patient Safety Tips of the Week for April 9, 2013 "Mayo Clinic System Alerts for QT Interval Prolongation"and June 10, 2014 "Another Clinical Decision Support Tool to Avoid Torsade de Pointes".

In our April 9, 2013 Patient Safety Tip of the Week "Mayo Clinic System Alerts for QT Interval Prolongation" we discussed one such CDSS tool that had been implemented at the Mayo Clinic (Haugaa 2013). In November 2010 the Mayo Clinic developed and implemented a system-wide QT alert system, called the pro-QTc system (see the prior column or the Haugaa article itself for details of the pro-QTc formula and scoring system). With some variation based on factors such as heart rate, a corrected QT interval (QTc) 500 msec or greater would trigger a notification alert to the ordering physician as a "semi-urgent finding" with a link to a Mayo website with guidance on management of such cases. They sent alerts to clinicians regarding about 2% of patients. For the population as a whole the QTc was a significant predictor of mortality. For each 10 msec

increment in QTc there as a 13% increase in mortality, independent of age and sex. The pro-QTc score was also a significant predictor of death and did so in a "dose-dependent" manner (i.e. each one-point increment in the pro-QTc score further increased mortality by a factor of 17%). On multivariable analysis only the number of QT-prolonging medications and electrolyte abnormalities were significant independent predictors of death. This again emphasizes the importance of recognizing drug combinations that may contribute to QT prolongation.

Then in our June 10, 2014 Patient Safety Tip of the Week "Another Clinical Decision Support Tool to Avoid Torsade de Pointes" we discussed another study which demonstrated that use of CDSS and computerized alerts can reduce the risk of QT interval prolongation (Tisdale 2014). One of the most important considerations is developing a system in which the risk of alert fatigue is minimized. We know from multiple studies done in the past that physicians override over 90% of computer alerts during CPOE (computerized physician order entry). To minimize the risk of alert fatigue and still accomplish your goal of reducing the risk to patients it is important to (1) deliver the alert to the right person (2) deliver alerts only for the most potentially serious events and (3) provide alternative options for the physician's response.

They system developed and implemented by Tisdale and colleagues did all three. First, the alerts first went to the pharmacist, who would then evaluate the situation and decide whether discussion with and recommendations for the physician were appropriate. Second, the thresholds to trigger the alerts were set at levels expected to minimize alert fatigue. And, third, the pharmacist responding to the alert would present the physician with some options for actions.

Their system would trigger an alert when the QTc interval was >500 ms or there was an increase in QTc of ≥60 ms from baseline. Their system also identified through the electronic medical record multiple other conditions or laboratory results that identified patients at higher risk for QT interval prolongation.

After implementation of the CDSS system the found a significant reduction in the risk of QT prolongation (odds ratio 0.65). In addition, they found a significant reduction in the prescription of non-cardiac drugs known to prolong the QT interval (especially fluoroquinolone antibiotics and intravenous haloperidol). Overall, 82% of alerts were overridden. That still compares favorably to the frequency with which other alerts are overridden. Most of the overrides were for cardiac drugs (eg. amiodarone or other anti-arrythmic drugs). The authors point out that overriding the computer alert did not mean that nothing was done. For example, even though the order for the drug may have been overridden the pharmacist and physician may have modified some other risk factor (eg. corrected an electrolyte disturbance or stopped another medication) or increased the frequency of QTc surveillance.

So what should your hospital or healthcare organization should be doing? We recommend the following:

- Define how you will measure and monitor the QT/ QT_c in your organization

- Decide how you will identify at-risk patients and monitoring frequencies for each risk category
- If a pre-op EKG is done, make sure someone pays attention to the baseline QT_c interval
- When starting drugs known to prolong the QT (eg. psychotropic drugs, methadone, amiodarone, etc.) make sure a baseline EKG is obtained and do reminders for when the QT should be remeasured
- Develop CPOE and decision support rules and surveillance to generate reminders to appropriate staff like those in the studies by Haugaa and Tisdale
- Consider sending the alerts to a clinical pharmacologist rather than directly to physicians; the clinical pharmacologist may then interact with the physician with suggestions for interventions
- Take appropriate actions as soon as you identify QT prolongation
- Establish patient educational materials to give at-risk patients at time of discharge
- Appropriate attention to those patients in outpatient settings who are begun on any of the drugs noted or have dose escalations of such drugs

Torsade de pointes is a relatively uncommon cause of sudden unexpected death but one that is potentially preventable. Being aware of the risk factors and having systems that identify when potentially dangerous drugs are being given to at-risk patients may potentially save lives.

Some of our prior columns on QT interval prolongation and Torsade de Pointes:

June 29, 2010 "Torsade de Pointes: Are Your Patients At Risk?"
February 5, 2013 "Antidepressants and QT Interval Prolongation"
April 9, 2013 "Mayo Clinic System Alerts for QT Interval Prolongation"
June 10, 2014 "Another Clinical Decision Support Tool to Avoid Torsade de Pointes"
April 2015 "Anesthesia and QTc Prolongation"

References:

CredibleMeds® website
https://crediblemeds.org/

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