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Patient Safety Tip of the Week

June 25, 2019 Found Dead in a Bed – Part 2

Last week's Patient Safety Tip of the Week "Found Dead in a Bed" focused on opioid-induced respiratory depression (OIRD) and the need for continuous physiological monitoring in patients at risk for OIRD. But not all instances of sudden, unexpected death in hospitals are due to OIRD.

Over the years, in our investigations and root cause analyses of cases of sudden unexpected death on general care floors, we've sometimes come across cases where we suspect Torsade de Pointes (TdP) as the underlying mechanism. Autopsy fails to demonstrate an obvious cause of death, so we often presume a cardiac arrhythmia likely led to death. Because such patients were not on continuous monitoring, we cannot be sure that torsade de pointes was the actual cause of death. However, we've seen prolongation of the QTc interval that suggests torsade as a potential cause. And, it is important to recognize these cases because this lethal arrhythmia is potentially preventable.

Torsade de pointes 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**. (See our earlier columns on the several methods of measuring the QT interval and criteria for QTc prolongation). 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. COPD was also recently added to the list of conditions associated with prolongation of the QTc interval, independent of electrolyte levels, comorbidities, or relevant medications (Zilberman-Itskovich 2019). More importantly, hospitalized patients 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 TdP than slow infusion.

Drugs commonly associated with torsade de pointes are haloperidol, methadone, thioridazine, amiodarone, quinidine, sotalol, procainamide, erythromycin, azithromycin, the antihistamine terfenadine and certain antifungals. But the list has grown by leaps and bounds in recent years. 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 extremely valuable 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**. Our October 10, 2017 Patient Safety Tip of the Week "More on Torsade de Pointes" discussed an FDA warning (FDA 2016) 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. Another study (Cook 2017) noted QTc prolongation related to an interaction between antifungal azoles and amiodarone. Another study (Lorberbaum 2016) noted that the combination of ceftriaxone (a cephalosporin antibiotic) and lansoprazole (a proton-pump inhibitor) will prolong the QT interval.

Several chemotherapeutic agents are known to prolong the QT interval, which can increase the risk of torsade de pointes (Zukkoor 2018). The most common are those of the tyrosine kinase inhibitor drug class, with vandetanib carrying the highest risk. And many chemotherapy regimens comprise of a number of supportive agents (eg. antiemetics, antidepressants, antihistamines, antibiotics) that may prolong the QT interval. The authors also note that other factors predisposing to QT interval prolongation are commonly seen in oncologic patients. For example, hypomagnesemia and hypokalemia due to poor oral intake or GI losses, elderly age, and impaired renal function are common in oncologic patients. And those with pre-existing cardiac disease are also more susceptible and may be on concomitant cardiac medications that potentiate QT prolongation and increase risk of torsade de pointes.

And don't forget that it's not just prescription and OTC drugs that may prolong the QT interval. Recent reports have focused on high volumes of energy drinks (Shah 2019) and grapefruit juice (Chorin 2019) as contributing to prolonged QTc intervals.

Tisdale et al. (Tisdale 2013) derived and validated a **scoring system** to predict QT interval prolongation in hospitalized patients, potentially identifying patients at risk for Torsade de Pointes. The Tisdale score could potentially be used to inform decisions about

patient monitoring and/or treatment. For example, just as we discussed in our June 11, 2019 Patient Safety Tip of the Week "Found Dead in a Bed" using the PRODIGY score to identify which patients at risk for OIRD (opioid-induced respiratory depression) should receive continuous physiological monitoring, you might use the Tisdale score to identify which patients at risk for Torsade de Pointes should receive monitoring.

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.

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 by Tisdale et al. (Tisdale 2014) which demonstrated that use of CDSS (clinical decision support systems) and computerized alerts can reduce the risk of QT interval prolongation. 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 they 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-arrhythmic 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.

In our April 9, 2013 Patient Safety Tip of the Week "Mayo Clinic System Alerts for QT Interval Prolongation" we discussed another 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.

A couple reviews (BMJ 2016, Li 2017) have discussed management issues in patients who have developed QTc prolongation, including discontinuation of the offending agent, consideration of alternate pharmacotherapy, assessment of the patient for any potential drug interactions that could lead to drug-induced QT prolongation, and evaluation for electrolyte abnormalities. They note an external defibrillator should always be readily available. Electrolyte abnormalities should be addressed. If the patient's potassium is low, it should be corrected. Magnesium sulfate should also be administered. The review by Li and Ramos (Li 2017) discusses the nuances of magnesium administration. It also discusses issues related to defibrillation if TdP actually occurs and use of temporary pacing, etc. while awaiting implantation of an automatic implantable cardioverter-defibrillator plus other special circumstances. The BMJ review (BMJ 2016) has a good discussion about when and how often to get EKG's when prescribing medications that may prolong the QTc in patients at risk.

So, we'd like to reiterate points from our earlier columns on what your hospital or healthcare organization should be doing to reduce the risk you'll find a patient "dead in a bed" from torsade de pointes:

- 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 (including which high risk hospitalized patients should receive continuous monitoring)
- 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 clinical decision support tools 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"
October 10, 2017 "More on Torsade de Pointes"

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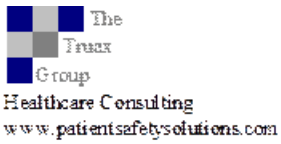

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