Patient Safety Tip of the Week

April 9, 2013

Mayo Clinic System Alerts

for QT Interval Prolongation

Torsade de Pointes (see our June 29, 2010 Patient Safety Tip of the Week "Torsade de Pointes: Are Your Patients At Risk?") 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.

In our Patient Safety Tips of the Week for June 29, 2010 "Torsade de Pointes: Are Your Patients At Risk?" and February 5, 2013 "Antidepressants and QT Interval Prolongation" we recommended development and implementation of CPOE tools and decision support rules and surveillance to generate reminders to appropriate staff regarding QTc (corrected QT interval) prolongation. Now the Mayo Clinic has reported its experience with implementation of just such a system (Haugaa 2013). In addition, they developed a useful scoring tool, the "pro-QTc score" to predict which patients are at risk of increased mortality with prolonged QTc intervals.

There are two key factors to consider that contribute to patients developing prolonged QTc intervals and torsade de pointes or other fatal arrhythmias:

1) Lack of awareness of the risk
2) No one could possibly recall by memory all the drugs that prolong the QT interval

To the first point, the risk for torsade de pointes is generally underappreciated. Cardiologists are more likely to be attuned to the risks for a number of reasons. They are always thinking about potential arrhythmias in the patients they treat. They also generally look at the ECG's on their own patients and are much more likely to pay attention to the QT interval. On the other hand, physicians on other services usually just look at the ECG report without attending to the QT interval duration. Unfortunately, many of the risk factors (especially the potentially modifiable ones) are seen in patients on services other than cardiology. Certainly the drugs capable of prolonging the QT interval are seen across all services. Some of those services, such as behavioral health, are less sophisticated from the "medical" standpoint unless they also have a dedicated internist or equivalent following each patient while hospitalized. And many of the electrolyte disturbances predisposing to torsade are also common in acutely and chronically ill patients seen on medical and surgical services.

To the second point, the list of drugs that often prolong the QT interval is now at over 100 drugs. 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 also has a list of drugs that prolong the QT interval and might possibly cause Torsade de Pointes and another list of drugs that have conditional risk (eg. only when combined with other drugs). Some drugs (eg. cisapride/Propulsid, a drug formerly used to promote GI motility) have actually been withdrawn from the market because of serious cardiac side effects, including prolongation of the QT interval and torsade de pointes.

In our June 29, 2010 Patient Safety Tip of the Week "Torsade de Pointes: Are Your Patients At Risk?" we referenced the 2010 AHA/ACCF statement on Torsade de Pointes (Drew et al 2010) which called for increased attention in early identification of patients with prolonged QT intervals who are at risk for torsade de pointes. So in November 2010 the Mayo Clinic developed and implemented a system-wide QT alert 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 analyzed over 86,000 ECG's in over 52,000 patients and sent alerts in 2% of cases. For 470 patients who had an isolated QTc of 500 msec or greater all-cause mortality was 19%, compared to 5% in patients with QTc intervals less than 500 msec. 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. Interestingly, mortality rates were higher in patients with noncardiac diagnoses.

The pro-QTc score included the following: female sex, QT-affecting clinical diagnoses and conditions, QT-prolonging electrolyte disturbances, and QT-prolonging medications (1 point given for each condition or drug). 58% of the 470 patients with isolated QTc of 500 msec or greater had at least one diagnosis associated with QT prolongation and, if

female sex were included as a risk factor 99% had at least one risk factor. 53% of these patients had either hypokalemia, hypomagnesemia or hypocalcemia. And 66% of these patients were on a medication known to prolong the QT interval (antidepressants were the most common drugs at 27%, followed by antiarrhythmics at 20% and antibiotics/antifungals at 20%). The mean pro-QTc score for these patients as a whole was 3.1.

The pro-QTc score was 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%). A pro-QTc score of 4 or greater predicted mortality with a hazard ratio of 1.72. On multivariable analysis only the number of QT-prolonging medications and electrolyte abnormalities were significant independent predictors of death. They note that if a patient had a QTc interval of 500 msec or longer and there were at least 4 QT-prolonging medications or QT-prolonging electrolyte disturbances, the mortality was 40%.

The authors describe a typical "perfect storm": a patient receiving an antidepressant is treated for an infection with an antibiotic having QT-prolonging potential and may have concomitant electrolyte abnormalities.

There are limitations to the study. It was a retrospective study, not a randomized controlled study. A substantial number of patients with congenital long-QT syndrome were included (because the Mayo Clinic is a referral center for such patients) but analysis excluding these patients did not alter their main findings. The authors of the Mayo study and the accompanying editorial (Mizusawa 2013) point out that the cause of death in patients was not known and it is likely that many did not die arrhythmic deaths. They also note that the pro-QTc score gave equal weight to all factors and that future modifications of that score might need to consider giving different weights to different factors (an example given is that the risk of torsade varies considerably for different drugs from the list of potentially QT-prolonging drugs). They also note that what the physicians did when they received an alert was not captured.

Overall, this is really a great contribution and shows that it is feasible to utilize readily available data to identify patients who may be at risk for torsade. We'd ultimately like to see integration of the QTc measurement and a scoring system like the pro-QTc scoring system into the CPOE system. Though we are always mindful of alert fatigue, it would be most valuable at the time of order entry to alert the physician that a drug he/she is about to order will likely further increase the QTc interval and put the patient at further risk of torsade.

Most importantly, it demonstrates that the major risk factors identified 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.

Also, since our last column on QT interval prolongation and the risk of torsade de pointes the FDA has issued a safety alert regarding QT interval prolongation and arrhythmia risk for azithromycin (FDA 2013). Though it has long been known that azithromycin is one of the drugs that can prolong the QT interval (we noted it in our June 29, 2010 Patient Safety Tip of the Week "Torsade de Pointes: Are Your Patients At Risk?") the FDA has looked at new information and determined that this risk is significant enough for azithromycin to issue the alert and update the drug labeling to strengthen the *Warnings and Precautions* section. Much of that new information came from a study published in the New England Journal of Medicine a year ago (Ray 2012). That study demonstrated an increase in cardiovascular deaths and all-cause deaths in patients treated with a 5-day course of azithromycin compared to treatement with amoxicillin, ciprofloxacin, or no drug. Moreover, the duration of the increased risk corresponded to the duration of the azithromycin therapy. The risks of cardiovascular death associated with levofloxacin treatment were similar to those associated with azithromycin.

During 5 days of azithromycin therapy there was a small absolute increase in cardiovascular deaths with 47 additional cardiovascular deaths per 1 million courses of azithromycin therapy compared to amoxicillin therapy. For patients in the highest decile of baseline risk of cardiovascular disease there were 245 additional cardiovascular deaths per 1 million courses.

However, the FDA alert appropriately recommends consideration of the potential benefits and risks of antibiotic choice given the context of the situation and also consideration that many of the alternative antibiotics may also prolong the QT interval.

Our June 29, 2010 Patient Safety Tip of the Week "Torsade de Pointes: Are Your Patients At Risk?" also discussed not only inpatient issues but also issues related to QTc prolongation and the emergency department, psychiatry, anesthesia, and surgery and the nuances of measuring the QT interval and the QT_c (corrected QT). In all settings it is important to consider not only the potential effect of various drugs but also underlying conditions and other contributing factors such as electrolyte disturbances. We had recommendations on what your hospital facilities should be doing:

- 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) 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
- 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

To those we obviously now recommend considering a system of alerts similar to that in the Mayo Clinic study and considering using a scoring system like the pro-QTc score.

Since the majority of the risk factors here are potentially modifiable or avoidable it is imperative that we put into place systems that will help early identification of patients at risk.

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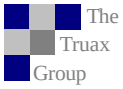

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