Patient Safety Tip of the Week

February 5, 2013

Antidepressants and

QT Interval Prolongation

In our June 29, 2010 Patient Safety Tip of the Week "Torsade de Pointes: Are Your Patients At Risk?" we discussed the risks of this potentially fatal syndrome in hospitalized patients. 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**. 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.

But, of course, the syndrome is not limited to hospitalized patients and we must remain vigilant for prolongation of the QT interval in outpatients as well. That is especially the case when dose escalations occur.

In our prior column we discussed the many drugs potentially implicated in prolonging the QT interval and potentially leading to Torsade de Pointes. But one class of drugs that had been relatively unrepresented was the antidepressant class. Then, in 2011 the FDA issued a warning about QT interval prolongation for citalopram (Celexa), later updated to restrict the dosage of citalopram to 20 mg. in patients older than 60 years and patients taking other drugs inhibiting cytochrome P450 2C19 (FDA 2012). The FDA also

recommends discontinuation of citalopram in patients found to have persistent QTc measurements greater than 500 msec.

Antidepressants, of course, are used not only in the treatment of depression but are also sometimes used for a wide variety of other clinical problems (eg. chronic pain, migraine, etc.).

Now a new study from the Partners HealthCare System has used innovative electronic health record technologies to assess the risk in patients taking both newer and older antidepressants (Castro 2013). The approach (see below) also has tremendous potential for other studies and for development of clinical decision support systems.

The authors were able to examine medical records for over 4 million unique patients within their system of hospitals and outpatient practices. They identified over 240,000 adult patients given at least one antidepressant.prescription and were then able to assess corrected QT intervals (QTc) from the electronic medical records in those patients who had electrocardiograms done. In many cases they had the opportunity to see the impact of dose escalations on the QTc. Plus they were able to assess a whole host of comorbidities and potentially confounding variables from the clinical records on these patients. They were able to identify a **dose-response association of QTc prolongation for citalopram, escitalopram, and amitriptyline**. This was not seen for other antidepressants. On the other hand, they found an association with QTc shortening for buproprion, a drug sometimes used in patients in whom first line antidepressants fail to produce anticipated result.

The authors, in discussing the implications of their findings, are quick to point out that QTc prolongation is only a surrogate measure for potential Torsade de Pointes and that the reported incidence of torsade in patients taking antidepressants is low. Nevertheless, they found that almost one in every five patients taking antidepressants had prolongation of the QTc interval and might be potentially at risk. Their findings might help in selection of individual drugs in certain patients. Importantly, it emphasizes the need for periodic monitoring in such patients, particularly when dose escalation is considered.

In our June 29, 2010 Patient Safety Tip of the Week "Torsade de Pointes: Are Your Patients At Risk?" we referenced the AHA/ACCF statement on Torsade de Pointes (Drew et al 2010). 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 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.

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

To those we obviously now would add appropriate attention to those patients in outpatient settings who are begun on any of the drugs noted or have dose escalations of such drugs.

One must keep in mind that the incidence of Torsade de Pointes and fatal arrhythmias is still quite low overall. Prolongation of the QTc interval is only a surrogate measure of the potential for such serious events. The potential benefits of many of these psychotropic agents may outweigh the risks of Torsade. But identifying the risk factors should at least flag such patients for closer monitoring during treatment with psychotropic drugs.

As we mentioned, the approach used by Castro and colleagues (Castro 2013) also has tremendous potential for other studies and for development of clinical decision support systems. They examined electronic health records using natural language processing (NLP) and machine-learning algorithms. Their article discusses the difficulties in identifying serious, but rare, adverse medication effects in the randomized controlled trials done prior to FDA approval or in the post-marketing surveillance studies done after approval. While results of studies using the techniques they used can really only demonstrate associations rather than determining definite cause-effect they really have unlimited potential to raise red flags that otherwise would take many years to appear.

They also have great potential for clinical decision support systems. Though we always need to keep in mind the risks of "alert fatigue", such systems could be used to prompt ordering of electrocardiograms in those patients on one of the higher risk drugs when a dose escalation occurs or when additional drugs are ordered. Or they could provide

reminders when serum potassium or magnesium levels should be considered in patients on such drugs. We described potential rules logic for some of those alerts in our June 29, 2010 Patient Safety Tip of the Week "Torsade de Pointes: Are Your Patients At Risk?"

This is really great work. Kudos to Castro and colleagues at Partners HealthCare not just for the messages in the specific study conducted but also for highlighting the potential use of such pharmacovigilance techniques for many other potential purposes.

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