Drug-Induced QT Prolongation And Torsades de Pointes

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INTRODUCTION

This column strays a bit from its regular format (no patient case is included) to discuss a drug-related adverse event that often goes undiagnosed or underdiagnosed. Drug-induced QT prolongation and torsades de pointes (TdP) are probably more prevalent than clinicians might think. Drugs by themselves can cause them in patients with underlying risk (to be discussed), and also in the setting of polypharmacy. This subject is a reminder to clinicians to always think about checking a patient's initial and follow-up electrocardiograms (ECGs) and/or obtaining or recommending follow-up ECGs for monitoring.

TdP, an uncommon polymorphic ventricular tachycardia, is characterized by a gradual change in the amplitude and twisting of the QRS complexes around the isoelectric line on an electrocardiogram.[1] TdP is associated with QTc prolongation, which is the heart-rate–adjusted lengthening of the QT interval. QT prolongation is one of the most infamous adverse drug reactions taught in pharmacy curricula because it can lead to sudden cardiac death.[2] Drug-induced prolonged repolarization of the heart is represented by a prolonged QT interval and can predispose a patient to develop this life-threatening arrhythmia. There is no threshold of QTc prolongation at which TdP is certain to occur. A QTc greater than 500 milliseconds (ms)

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Welcome to the Pharmacovigilance Forum, where we report on interesting adverse drug reactions (ADRs), including drug-induced disease. All pharmaceuticals carry a risk of ADRs, whether they are new and improved, generic agents, older brand products, complex biologics, or biosimilars. Each Pharmacovigilance Forum discusses noteworthy topics related to ADRs in the clinical realm. Every medication has the potential to cause disease, but clinicians are often slow to recognize drug therapy as an etiological factor. I encourage anyone with a potential case or related idea to contact me at michekauf@yahoo.com; to publish ADRs here or elsewhere; and to report ADRs to the Food and Drug Administration's MedWatch program.

—Michele B. Kaufman

has been associated with a twofold to threefold higher risk for TdP, and each 10-ms increase contributes to approximately a 5% to 7% exponential increase in risk.[3,4] QT prolongation can increase hospital length of stay and all-cause mortality in patients. In addition, many drugs have the potential to cause QT prolongation and/or TdP, either alone or in a drug interaction situation.

QT PROLONGATION, TDP, AND THE FDA

Drug interactions involving the inhibition of metabolism have contributed to the removal of a number of medications from the U.S. market.[5] For example, the first two nonsedating antihistamines—terfenadine (Seldane, Hoechst Marion Roussel) and astemizole (Hismanal, Janssen)—were approved by the Food and Drug Administration (FDA) in 1985 and 1998, respectively, and both were considered significant improvements in allergy treatment.[6] Shortly after the approval of terfenadine, however, the FDA began receiving case reports of TdP in patients treated with the agent along with certain antibiotics, as well as in patients with significant hepatic dysfunction.[7] It was discovered that terfenadine metabolism was inhibited by the cytochrome P450 (CYP) 3A4 pathway, leading to very high levels of terfenadine, causing delayed cardiac repolarization (prolonged QT interval), and increasing the risk of ventricular tachyarrhythmia, including TdP. The FDA began to raise adverse drug interaction aware-

ness through "Dear Healthcare Professional" letters (in 1990, 1992, and 1996), and warning label updates were used as alerts prior to market withdrawal. Terfenadine was removed from the market in early 1998, once the safer, nonsedating antihistamine fexofenadine became available; it did not prolong the QT interval. Similarly, prior to the availability of fexofenadine, astemizole was approved by the FDA in 1998, but its manufacturer voluntarily withdrew it from the market in 1999 due to safety issues, most notably QT prolongation following inhibition of hepatic metabolism by other drugs.[8]

Cisapride (Propulsid, Janssen), a prokinetic agent used as a treatment for gastroesophageal reflux disease, was approved by the FDA in 1993 and withdrawn from the market worldwide in January 2000 due to the occurrence of QT prolongation, ventricular arrhythmia, and sudden cardiac death due to inhibition of cisapride metabolism by CYP3A4 from other drugs.[5,9]

Droperidol (Inapsine, Taylor Pharmaceuticals) was approved by the FDA in 1988 as an injectable antiemetic for patients undergoing surgical and diagnostic procedures.[10] Droperidol subsequently underwent labeling updates in the form of a boxed warning in late 2001 due to QT prolongation and TdP, including deaths.[11] Following this warning, droperidol use declined precipitously. Subsequently, safer antiemetics were approved by the FDA and utilized.[6]

PATHOPHYSIOLOGY

The proposed cellular mechanism of drug-induced prolonged QT interval involves inhibition of the rapid component of the delayed rectifier potassium current (IKr).[1] Blocking IKr leads to prolongation of the ventricular action potential duration, leading to an excess sodium influx or a decreased potassium efflux. This excess of positively charged ions leads to an extended repolarization phase, resulting in a prolonged QT interval and causing arrhythmias such as TdP. This TdP trigger is seen as a premature ventricular complex (PVC) that is generated during the prolonged repolarization phase, also known as the R-on-T phenomenon.[2] In contrast to ventricular fibrillation, TdP is a unique ventricular arrhythmia because it can spontaneously end. However, it is possible for TdP to degenerate to ventricular fibrillation and cause sudden cardiac death.[2]

QTc prolongation may be acquired (secondary) or congenital (primary). Many distinct genetic mutations and polymorphisms lead to congenital long QT syndrome, which occurs in about 0.0005% of live births.[12] Acquired QTc prolongation is almost always caused by drugs.

OVERVIEW

As noted above, a number of medications have been withdrawn from the U.S. market due to the causation of prolonged QT interval and/or TdP. Medications that directly affect the electrophysiology of the heart can prolong the QT interval. Some medication classes, notably antiarrhythmics and fluoroquinolones, indirectly affect the heart via heterogeneity of transmural ventricular repolarization among the three principal cell types of the heart: endocardial, myocardial, and epicardial cells.[13] The amplification of spatial dispersion of repolarization within the ventricular myocardium is thought to generate the principal arrhythmogenic substrate in both acquired and congenital long QT syndrome.[13] For this reason, medications that prolong the QT interval via uniform IKr inhibition across the ventricular myocardium, such as amiodarone and verapamil, have a low incidence of TdP.[1]

The development of TdP is multifactorial. The factors that have been associated with an increased risk of TdP include: congenital long QT syndrome;

Table 1 Risk Factors for Torsades de Pointes[1,12]
• Older than 65 years of age
• Bradycardia
• Congenital long QT syndrome or genetic polymorphisms
• Diuretic treatment*
• Electrolyte abnormalities (i.e., hypokalemia, hypomagnesemia, hypocalcemia)*
• Female gender
• Genetic predisposition
• Heart disease: myocardial infarction, congestive heart failure, left ventricular failure, heart failure with reduced ejection fraction
• Hepatic drug metabolism impairment
• Increased QTc interval > 60 ms compared to the pretreatment value
• QTc > 500 ms
• QT-prolonging drugs already being used, rapid IV infusion of QT-prolonging drugs, inadequate renal dosing of QT-prolonging drugs in AKI or CKD, drug interactions*
• Recent cardioversion

AKI = acute kidney injury; CKD = chronic kidney disease; IV = intravenous; ms = milliseconds.

* Modifiable risk factors.

Table 2 Common Drugs Known to Cause Torsades de Pointes[11,18]	
Class	Examples
Antiarrhythmics	Disopyramide, procainamide, quinidine, sotalol
Macrolides	Azithromycin, clarithromycin, erythromycin
Fluoroquinolones	Ciprofloxacin, levofloxacin, moxifloxacin
Antifungals	Fluconazole, ketoconazole, pentamidine, voriconazole
Antipsychotics	Haloperidol, thioridazine, ziprasidone
Antidepressants	Citalopram, escitalopram,
Antiemetics	Dolasetron, droperidol, granisetron, ondansetron
Opioids	Methadone
Miscellaneous	Cocaine, cilostazol, donepezil

a QTc interval greater than 500 ms; a QTc interval increased by more than 60 ms compared with pretreatment value; genetic polymorphisms in genes encoding ion channels; a history of drug-induced TdP; bradycardia; congestive heart failure with a reduced ejection fraction; myocardial infarction; female gender; age older than 65 years; structural heart disease; chronic renal/hepatic insufficiency; electrolyte abnormalities such as hypokalemia, hypomagnesemia, or hypocalcemia; diuretic treatment; concurrent use of more than one QT-prolonging drug; intravenous (IV) administration of QT-prolonging medications; and rapid infusion of QT-prolonging medications.[1,14] The diagnosis of TdP is made based on ECG findings. A list of the risk factors for TdP can be seen in Table 1.[1,12]

INCIDENCE

There is an extensive list of medications that can prolong the QT interval and cause TdP, some of which are listed in Table 2. Many of these drugs are common in clinical practice, such as antiarrhythmics, antimicrobials, antipsychotics, antihistamines, and antiemetics.[2] Despite this formidable list of agents, the only classes of medications with incidence data of up to 10% are Class Ia (disopyramide, quinidine, procainamide) and Class III (sotalol, dofetilide, ibutilide) antiarrhythmic agents.[1] In addition to the antiarrhythmic agents, there are numerous case reports and case series confirming the arrhythmogenic potential of thioridazine, methadone, tricyclic antidepressants, and haloperidol.[12–17] The list of drugs known to cause TdP that require a dose adjustment for patients with acute kidney injury or chronic kidney disease include: ciprofloxacin, disopyramide,

dofetilide, flecainide, fluconazole, levofloxacin, procainamide, and sotalol.[12] An extensive and continuously updated list of QT-prolonging medications can be accessed online at www.crediblemeds.org or through the CredibleMeds mobile app.[18] CredibleMeds is a nonprofit, university-based, federally funded Center for Education and Research on Therapeutics, with a mission to foster safe medication use. CredibleMeds develops educational and research programs and provides resources for medical professionals, researchers, and consumers. It has built and utilizes a novel, risk-stratification–based approach to reducing medication harm and drug–drug interactions, particularly for those drugs that prolong the QT interval and increase the risk for TdP.

SYMPTOMS AND DIAGNOSIS

The symptoms of TdP are similar to other tachyarrhythmias related to heart rate, blood pressure, and cardiac output. Sometimes TdP is self-limiting and can spontaneously resolve. Other times, it can degenerate into ventricular fibrillation and death. Some signs and symptoms associated with drug-induced TdP include: TdP on ECG (polymorphic ventricular tachycardia in the setting of a prolonged QTc interval); a "long–short" initiating sequence on the ECG (a ventricle extrasystole [first beat: short], followed by a compensatory pause while the following beat [second beat: long] has a longer QT interval); chest pain; dizziness; hypotension, light-headedness; near syncope; palpitations; seizure; shortness of breath; syndrome of sudden cardiac death; and tachycardia.[1,19]

A patient presenting with any of the above symptoms should be evaluated for TdP. The diagnosis is made based on ECG findings with the characteristic "twisting of the points:" twisting of the wide QRS complexes around the isoelectric baseline. Drug-induced TdP can occur at different times while the patient is receiving the offending oral agent(s). When TdP occurs following IV therapy, it usually corresponds with the expected time of the medication's peak concentration. In addition, any patient who presents to the emergency department following an overdose of a QT-prolonging drug should be evaluated for TdP. Other conditions to consider in the differential

diagnosis for drug-induced TdP include: atrial fibrillation, atrial flutter, atrial tachycardia, atrioventricular node re-entrant tachycardia, monomorphic ventricular tachycardia, non-TdP polymorphic ventricular tachycardia, and sinus tachycardia.[19] These tachyarrhythmias need to be excluded by evaluating the ECG prior to diagnosing drug-induced TdP.

MANAGEMENT

Drug-induced QT prolongation is defined as a QTc of 500 ms or greater or an increase of 60 ms or greater in the QT interval compared with the premedica-

tion baseline interval.[1] Attempts should be made to correct any modifiable risk factor. The first three management techniques in the setting of drug-induced QT prolongation/TdP are: 1) discontinue the offending agent(s) and consider alternate pharmacotherapy; 2) assess the patient's chart for any potential drug interactions that could lead to drug-induced QT prolongation and/or TdP; and 3) evaluate the patient for electrolyte abnormalities. A list of common drug interactions can be seen in Table 3. If these three precautionary measures fail to prevent TdP, an external defibrillator should always be readily

Table 3 Common Pharmacokinetic Drug Interactions Associated With Torsades de Pointes[12]

Inhibition of CYP3A4		Inhibition of CYP2D6	
Inhibitors	**Substrates**	**Inhibitors**	**Substrates**
Antifungals • Itraconazole • Ketoconazole • Posaconazole • Voriconazole **Macrolides** • Erythromycin • Clarithromycin • Azithromycin **Protease inhibitors** • Atazanavir • Darunavir/ritonavir • Fosamprenavir • Indinavir • Nelfinavir • Saquinavir • Tipranavir	Amiodarone Disopyramide Dofetilide Pimozide	**Neuropsychiatrics** • Bupropion • Duloxetine • Fluoxetine • Paroxetine **Antifungal** • Terbinafine	Flecainide Quinidine Thioridazine

CYP = cytochrome P450

Table 4 Tisdale Risk Score[12]

Risk Factor	Points	QTc Interval Risk Score Stratification	
		Risk Score Category	**Risk Score**
Age ≥ 68 years	1	Low	< 7
Female gender	1		
Loop diuretic	1		
Serum potassium ≤ 3.5 mEq/L	2		
Admission QTc ≥ 450 ms	2	Moderate	7–10
Acute myocardial infarction	2		
≥ Two QTc-prolonging drugs	3		
Sepsis	3	High	> 11
Heart failure	3		
One QTc-prolonging drug	3		
Maximum Risk Score	**21**		

available in order to administer direct-current cardioversion (DCCV) if necessary. Other recommended pharmacotherapy should be based on the patient's clinical presentation.[1] The Tisdale score can be used to assess which patients are at higher risk for developing TdP (Table 4).[12]

The administration of the offending agent(s) should be discontinued, and electrolyte abnormalities should be addressed. If the patient's potassium is low, it should be corrected. Magnesium sulfate should also be administered at 1–2 g diluted in 50–100 mL dextrose 5% in water as an IV piggyback over five to 60 minutes.[1] The mechanism behind the benefit of magnesium sulfate in treating TdP is unknown. Hypokalemia must initially be corrected before magnesium can be repleted. Following the administration of magnesium sulfate, the patient's heart may convert back to normal sinus rhythm without a noticeable change in the QTc; magnesium does not shorten the QTc interval significantly and has no significant role in the management of long QT syndrome.[1,5] The rate of administration varies depending on the patient's clinical status.[20]

When TdP develops and does not spontaneously end in a patient who is hemodynamically unstable or in cardiac arrest (i.e., ventricular fibrillation), the patient should receive immediate DCCV or defibrillation followed by a magnesium sulfate 2 g IV push over one to two minutes.[1] If the patient is conscious or hemodynamically stable, DCCV is withheld and IV magnesium sulfate 2 g is given slowly over 15 minutes to avoid the adverse effects of rapid magnesium administration.[21]

Magnesium is given irrespective of the serum magnesium level and can be repeated every five to 15 minutes if TdP persists.[1] It is important to monitor the patient closely for signs and symptoms of hypermagnesemia, such as bradycardia, hypotension, and muscle weakness.

There is a correlation between abnormal electrolytes and arrhythmogenicity.[22] While there are currently no data to support the administration of potassium for the treatment of TdP, administration of potassium is considered an important adjunct to magnesium sulfate for the prevention of TdP.[20] Potassium repletion should be maintained at 4.5–5.0 mmol/L,

and the target magnesium level should be greater than 1.7 mg/dL.[23]

Temporary transvenous ventricular pacing at rates greater than 100 beats per minute (bpm) can be utilized until the patient receives a permanent pacemaker or automatic implantable cardioverter-defibrillator.[20] Overdrive pacing may also be used temporarily with isoproterenol, an effective beta$_1$ and beta$_2$ agonist, given as a continuous IV infusion at 2–10 mcg per minute and titrated to 100 bpm.[1] Despite its efficacy, isoproterenol is an expensive agent that may increase myocardial oxygen demand and lower systemic vascular resistance, resulting in ischemia and potential hemodynamic compromise.[24] The rationale for pacing is to intervene on the prolonged repolarization caused by the offending agents to prevent the development of PVCs that may trigger TdP.[20]

Special circumstances may require additional therapies. Quinidine-induced TdP requires the administration of sodium bicarbonate to alkalinize the serum and increase protein binding.[25] In the setting of sotalol-induced TdP that is refractory to standard therapy such as magnesium sulfate and overdrive pacing, hemodialysis can be used to accelerate drug clearance and to revert the patient back to normal sinus rhythm.[26]

CONCLUSION

The development of TdP is rare and multifactorial, with drugs or drug interactions being the most likely culprits. Preventive measures include diligent QTc monitoring, electrolyte repletion, and assessment of potential aggravating drug use and/or drug–drug interactions. Management of TdP can involve DCCV, IV magnesium sulfate, transvenous/pharmacological pacing, and electrolyte repletion.

Pharmacists are important members of the health care team, especially when it comes to minimizing and preventing drug-induced disease. Pharmacist knowledge of the many drugs and drug interactions that cause or potentially cause QT prolongation and/or TdP, as well as which renally eliminated QT-interval prolonging drugs require dose adjustments in patients with renal impairment, is critical to our role in treating patients. Utilization of a risk-scoring system may be a viable means to iden-

tify patients at risk of TdP. This knowledge improves patient care and overall outcomes.

REPORTING ADVERSE DRUG REACTIONS

All ADRs should be reported to MedWatch at 1-888-INFO-FDA (1-888-463-6332) or online. The FDA 3500 Voluntary Adverse Event Report Form can be accessed easily online for reporting ADRs at www.fda.gov/Safety/Medwatch/HowToReport/ucm085568.htm.

The FDA is interested in serious reports that include any of the following patient outcomes: death; life-threatening condition; initial hospitalization; prolonged hospitalization; disability or permanent damage; congenital anomalies or birth defects; and other serious conditions for which medical or surgical intervention is needed to prevent one of the aforementioned outcomes. The FDA is also interested in any unlabeled ADRs for new drugs.

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