Wyoming Drug Utilization Review

QT Prolongation, Torsades de Pointes, and Drug Safety

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Introduction

Among industrialized nations sudden cardiac death (SCD) is a major cause of mortality, accounting for approximately 50% of all deaths from cardiovascular disease and about 20% of total mortality.[1] Almost all cases of SCD are caused by acute ventricular arrhythmias (80-85%), and most occur in individuals who were not known to be at risk.[1] One of the most important known risk factors for ventricular arrhythmia is the prolongation of ventricular repolarization, measured as a prolonged QT interval.[1,2] "Prolongation of ventricular repolarization may result in early after depolarizations (EAD), which in turn may induce re-entry and thereby provoking *torsade de pointes* and fatal ventricular arrhythmia."[1]

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Torsades de pointes

The term *torsades de pointes* (TdP) is used to describe a polymorphic ventricular arrhythmia that occurs only in the presence of a prolonged QT interval.[3] TdP is one of the most common arrhythmias associated with cardiotoxic drugs, and although the incidence of TdP is unknown, its occurrence is relatively rare in the general population.[3] TdP is often unpredictable and can be asymptomatic, or cause palpitations, syncope, and dizziness, however, the first symptom might be SCD.[2]

QTc Interval

Although accurate predicting of the risk of TdP is important, currently there are no blood tests nor any other type of examination that is capable of accurately predicting which patients will develop TdP.[2] The length of the QT interval is used as a surrogate marker to assess the duration of ventricular depolarization and repolarization as a way to predict a patient's risk for developing TdP. The QT interval is measured in milliseconds (ms), is usually adjusted for heart rate (QTc), and represents the time it takes for the heart to return to a resting state after a contraction.[1,3] A QT interval is considered prolonged if it is > 460 ms for females or > 440 ms for males.[3]

The accuracy of using QTc as a marker for the risk of developing TdP and SCD is considered imprecise and is associated with measurement inaccuracies, false positives, and a lack of standardization regarding what types of leads or heart rate corrections should be used.[2] Accurately measuring the QT interval requires specialized training, and one survey has suggested "that only 36% of physicians were able to correctly measure the QT interval."[2]

Despite of all the difficulties associated with measuring QT intervals, the QTc interval remains the most widely used surrogate marker for estimating a patient's risk of developing TdP.[2]

Electrophysiology of the heart

A normal cardiac action potential is determined by a delicate balance of inward depolarizing and outward repolarizing ion currents.[1,2] Lengthening of the QT interval can occur due to prolongation of either the depolarization or repolarization processes. However, because repolarization makes up the majority of the QT interval, it is usually in this phase the QT interval is lengthened.[2] The most important ion channels associated with repolarization are the potassium channels, which serve to counteract the effects of the influx of calcium and sodium. A change in the function of the ion channels can upset the balance and lead to an increased repolarization time.[2] Almost all QT-prolonging drugs act by blocking the fast delayed rectifier potassium channel (IK_r), which results in slowing of the conduction velocity and broadening of the QRS complex.[1,2]

Risk Factors

The majority of cases of drug-induced TdP occur in patients with several risk factors for developing TdP, and

continued on page 3

P & T Committee Meeting Update

The P&T Committee met for its quarterly business meeting on May 17, 2012. Highlights of this meeting include:

The following prior authorization was approved:

Kalydeco will require prior authorization. All requests will be referred to Dr. Bush for review and management.

Rectiv will require prior authorization with a trial and failure of commercially available, generic nitroglycerin ointment required for approval.

Korlym will be allowed for those patients with a diagnosis of hyperglycemia secondary to hypercortisolism in adult patients with type 2 diabetes or glucose intolerance who have failed surgery or are not surgery candidates.

Compounded topical products for neuropathic pain will require prior authorization with a referral to Dr. Bush for review. Requests for compounded topical ketoprofen products will be denied and referred to commercially available topical NSAIDs.

Oxecta will require prior authorization with a history of or high risk for opiate abuse necessary for approval.

All proposed prior authorization criteria will be posted for public comment at *www.uwyo.edu/DUR*. Comments may be sent by email to alewis13@uwyo.edu or by mail to: Wyoming Drug Utilization Review Board, Dept. 3375, 1000 E. University Avenue, Laramie, WY 82071. Comments should be received prior to June 30, 2012.

The next P&T Committee meeting will be held August 30, 2012 in Cheyenne. An agenda will be posted approximately two weeks prior to the meeting.

New Medicaid Pharmacy Program Manager

Hello! I am Cori Cooper, and in April I started as the Medicaid Pharmacy Program Manager for the State of Wyoming. I graduated from the University of Wyoming in 2002 with my Doctor of Pharmacy degree, and have since worked as an instructor for the University of Wyoming, a staff pharmacist at CRMC, and then at the VA for a little over eight years, serving as an outpatient and inpatient pharmacist, the Geriatric Specialist and, most recently, the Pharmacy Benefits Manager. I am married and have two young daughters, ages 2 and 6. I am a native of Cheyenne with many ties to the local community and the state, and I feel very fortunate to be serving Wyoming and its citizens. I look forward to working with pharmacists and providers to continue making excellent healthcare available to all those who live in this great state!

Table 1: Drugs that may increase QT interval or induce torsades de pointes[5]

Antiarrhythmics	
Amiodarone	Quinidine
Disopyramide	Sotalol
Procainamide	Dofetilide
Antibiotics	
Macrolides	Trimethoprim-
Fluoroquinolones*	Sulfamethoxazole
Antidepressants	
Desvenlafaxine	Citalopram*
Fluoxetine*	Escitalopram
Mirtazapine*	Trazodone
Paroxetine*	Venlafaxine*
Sertraline*	Amitriptyline*
Antipsychotics	
Aripiprazole*	Ziprasidone*
Haloperidol	Clozapine
Olanzapine*	Quetiapine*
Risperidone*	Paliperidone*
Antihistamines	
Cetirizine*	Diphenhydramine
Hydroxyzine	
Opioid agonists	
Oxycodone*	Methadone
Antifungals	
Fluconazole	Itraconazole
Ketoconazole	Voriconazole
Other	
Albuterol*	Promethazine
Salmeterol*	Ondansetron
Pseudoephedrine*	Moexipril/HCTZ*
Ventolin*	Methylphenidate
Metoclopramide	Lithium

* Denotes drugs on the Wyoming Medicaid Preferred Drug List

rarely in patients with only one risk factor.[2] A major risk factor for developing TdP or SCD is congenital long QT syndrome, (LQTS) which involves a mutation that either increases sodium or calcium channel function, or reduces potassium channel function, all of which increase the QT interval.[2] Patients with certain genetic variations in drug metabolizing enzymes (including CYP2D6 or CYP3A4) may also be at increased risk due to the poor metabolizing of QT-prolonging drugs, resulting in increased exposure for a given dose.[2]

The incidence of acquired QT syndrome, however, is much higher than the incidence of congenital LQTS, and is usually associated with the use of specific QT-prolonging drugs.[1] Normally, the heart is able to compensate for minor changes in ion channel function, a phenomenon known as repolarization reserve. Many risk factors are capable of reducing this intrinsic repolarization reserve and can predispose patients to TdP. [2] Other risk factors include structural heart disease, electrolyte disturbances, female gender, increased age, bradycardia, renal or hepatic disease, concomitant use of more than one QT-prolonging drug, and drug-drug interactions.

Drug-induced TdP

A number of medication classes have been associated with prolonging the QT interval, including, but not limited to, some antibacterials, antipsychotics, antihistamines, and antiarrhythmias.[1,2] Table 1 provides some of the drugs associated with prolonging the QT-interval or inducing TdP.[1-3] (For more information and more extensive drug lists visit www.azcert.org[4]) Concomitant use of more than one QT-prolonging drug could result in an additive QT-prolonging effect, and drugs eliminated by only a single route are subject to accumulation if that route is blocked.[3] Even at normal doses, the presence of renal or hepatic insufficiency, or the inhibition of metabolism of QT prolonging drugs may increased the plasma concentration and thereby increase the risk of QT prolongation.[2]

Clinical Recommendations

An assessment of cardiac safety should be made for patients who will be started on potentially QT-prolonging drugs, and should identify if the patient has a family history of diabetes, cardiovascular disease, palpitations, arrhythmia, or SCD at a young age.[2] Ideally an ECG should be obtained before initializing a new drug and again once the drug has reached a steady state. While this may not be possible for every patient, it is most important for patients who already have several risk factors for TdP, or who are already on QT-prolonging drugs.[2] If a case of abnormal or prolonged QT occurs, it is important to rule out other potential causes including cardiovascular disease and electrolyte imbalances before permanently discontinuing drug therapy.[2] An increase in QTc interval of >60 ms from baseline or a QTc interval reading > 500 ms should result in discontinuation of drug therapy, unless benefits from therapy with the causative agent clearly outweigh the increased risk of TdP.[2] "Drugs with severe QTc interval-prolongation should be avoided in those with known cardiovascular disease, prior myocardial infarction, cardiomyopathy, electrolyte disturbances or hypertension, as their extent of QTc interval prolongation may be more pronounced than in healthy people."[2]

Conclusion

Sudden cardiac death is a leading cause of mortality in the developed world. Although imperfect, the QTc interval is the most commonly used diagnostic tool for determining risk of TdP. Several risk factors for TdP have been identified, and most cases of TdP are a result of a combination of risk factors. Most drugs that prolong the QTc block potassium channels and delay repolarization. Any potential risk associated with the use of a known QT-prolonging drug should be weighed with its therapeutic efficacy, and alternative agents should be used in patients at a higher risk for TdP.

References

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2. Van Noord C, Eijgelsheim M, Stricker BH. Drug- and non-drug associated QT interval prolongation. Br J Clin Pharmacol. 2010;70:16-23.
3. Killeen M. Drug-induced arrhythmias and sudden cardiac death: implications for the pharmaceutical industry. Drug Discov Today. 2009;14:589-597.
4. Arizona Center for Education and Research on Therapeutics. Drugs with risk of torsades se pointes. Arizona CERT website. Available from: http://www.azcert.org/medical-pros/drug-lists/list-01.cfm?sort=Generic_name. Accessed: February 27, 2012.
5. Cupp M. PL Detail-document: drug induced long QT interval. Pharmacist's Letter/Prescribers Letter. 2012;28:280111.

2012 P & T Committee Meeting Dates

August 30, 2012
November 15, 2012

9 am - 1 pm
Laramie County Community College, Cheyenne
All meeting dates and times are subject to change.

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In This Issue

QT Prolongation, Torsades de Pointes, and Drug Safety
P & T Committee Meeting Update
New Medicaid Pharmacy Program Manager
2012 P & T Committee Meeting Dates

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