Pharmacy FAQ

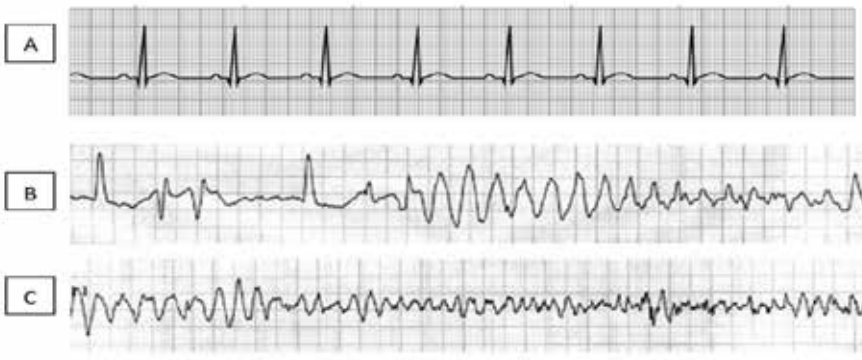
QT Prolongation in Oncology

1. What is QT prolongation and why is it a concern?

On an electrocardiogram (ECG or EKG) the QT-interval represents the time, in milliseconds (ms), it takes for the heart ventricles to depolarize (contract) and repolarize (recover). Certain drugs can delay ventricular repolarization, most often by interfering with ion currents across myocardial cell membrane potassium channels. This delayed repolarization prolongs the QT-interval, also known as drug-induced QT prolongation.[1,2,3]

It is a concern because QT prolongation is a risk factor for developing Torsades de Pointes (TdP), a potentially life-threatening ventricular tachycardia. QT prolongation can allow myocardial electrical disturbances to develop into TdP, which is usually self-limiting and resolves spontaneously. However, if unresolved, TdP can further degenerate into ventricular fibrillation (VF) and sudden cardiac death (see Figure 1). Post-marketing surveillance case reports of this nature have resulted in black box warnings in drug monographs (e.g., methadone), or drugs being removed from the market (e.g., cisapride), and have made QTc testing mandatory during drug developement.[1,3,4,5,6,7] Note that drug-induced QT prolongation is a rare side effect, and it does not commonly lead to TdP.[1]

Figure 1. ECGs of Normal QT-interval, QT prolongation degenerating into TdP, and VF



A. Normal QT Intervals*
B. Long QT-intervals degenerating into TdP (which is named for its "twisting" appearance on an EKG)**
C. TdP degenerating into VF **

*Reproduced with permission from the University of New Mexico Hospitals Department of Clinical Education
**Reproduced from Drug induced QT prolongation and torsades de pointes, Yee Guan Yap, A John Camm, 89, Figure 1, 2003 with permission from BMJ Publishing Group Ltd.

2. What is a corrected QT-interval?

The QT-interval is inversely proportional to the heart rate – it gets longer with a slower heart rate. So a corrected QT-interval (QTc) estimated at a heart rate of 60 beats per minute (bpm) is used to allow comparison of QT values over time and across different heart rates. There are several formulas used to calculate the QTc-interval, with Bazett's formula being the most commonly used in BC. It provides an adequate estimate for average heart rates but may over-/under-correct at more extreme heart rates.[1,3,4]

The effect most drugs have on the QT-interval is concentration dependent, so it should be measured when the drug is at peak plasma concentration or steady-state.[1,3,5,6]

3. What are the risk factors for drug induced QT prolongation or TdP?

Most reported cases of drug-induced TdP involve at least one other risk factor, besides the drug, and over 70% involve at least two other risk factors.[1,3]

Unmodifiable risk factors for drug-induced QT prolongation or TdP include female gender, advanced age, genetic predisposition (congenital long QT, family history of sudden cardiac death, previous history of TdP), structural heart disease/left ventricular dysfunction, impaired elimination due to renal/hepatic dysfunction.

Potentially modifiable risk factors for drug-induced QT prolongation or TdP include hypokalemia, hypomagnesia, bradycardia (e.g., recent cardioversion for atrial fibrillation, recent initiation of sotalol), drug interactions, high concentrations of QT prolonging drug(s) (e.g., high dose or rapid IV infusion), and nutritional issues (e.g., anorexia, extreme vomiting/diarrhea).[1,3,4]

Patients with QTc > 500 ms, or an increase of > 60 ms from baseline, are considered at increased risk for TdP.[1,4,6]

4. What symptoms do patients present with?

Symptoms may include palpitations, dizziness, light-headedness, fainting, seizures, and cardiac arrest.[1,2,3,4,6]

Some patients may present with recurrent syncope, which can sometimes be misdiagnosed as seizures.

5. What is a reputable resource to identify QT prolonging drugs?

Credible Meds (formerly Qtdrugs.org)

This website has an OncoSupportTM Drug List section that focuses on oncology drugs under the For Healthcare Providers tab. The website is free but requires online registration.

6. Which oncology drugs are associated with the highest risk for QT prolongation and Torsades de Pointes (TdP)?

The oncology agents most associated with risk for QT prolongation and TdP include anagrelide, arsenic trioxide, oxaliplatin, and vandetanib.

Supportive medications used for cancer patients can also cause QT prolongation. The antiemetics ondansetron, domperidone, chlorpromazine, and droperidol are most associated with risk for TdP. The opioid analgesic methadone also has known risk.

Additionally, androgen deprivation therapy (as a class) for men with prostate cancer may possibly increase QT prolongation risk due to consequences from reduced testosterone levels.[7]

Other non-oncology drugs (e.g., certain antiarrythmics, antimicrobials, antidepressants, and antipsychotics), herbal products, or foods (e.g., grapefruit juice) taken by cancer patients should also be considered. They may be directly associated with a higher risk for TdP, or indirectly increase the risk for TdP (e.g., via cytochrome P450 mediated drug interactions, or via causing bradycardic effects or electrolyte abnormalities).

Co-administration of multiple directly or indirectly QT prolonging drugs causes additive risk. A careful review for drug interactions is recommended.[1,2,3,4,8]

7. What interventions and monitoring recommendations can pharmacists make to reduce the patient's risk for Torsades de Pointes (TdP)?

Assess patients for additional risk factors for QT prolongation before starting a QT prolonging drug. Reduce/correct any modifiable risk factors IF POSSIBLE:[1,2,3,4]

- Hold/discontinue concomitant drug(s) that may cause or enhance QT prolongation. [Caution - drugs such as antidepressants may require tapering]
- Use the lowest dose for the shortest duration possible
- If applicable, correct electrolyte abnormalities – e.g., K^+ and Mg^{2+}

Consider ECG monitoring or cardiologist assessment for higher non-modifiable risk or symptomatic patients. For example, for patients concurrently on multiple drugs known to have a risk of TdP, it is reasonable to request a baseline ECG, and then repeat the ECG at the time of expected drug peak level. Further periodic ECG monitoring may be warranted while on the QT-prolonging drug(s), especially if QT prolongation is observed.[1,2,3,8,9,10]

Patients with QTc > 500 ms, or an increase of > 60 ms from baseline, are considered at increased risk for TdP and action should be taken.[1,2,3,4,5,6,10]

- Consult applicable manufacturer instructions
- Correct electrolyte abnormalities aggressively
- Correct potentially aggravating drug interactions
- Escalate ECG monitoring
- Consider modifying QT-prolonging drug(s) therapy
- Consult cardiologist

Patients should be educated to:

- Monitor for possible symptoms, such as palpitations, dizziness, light-headedness, fainting, and seizures
- Keep a list of all the medications they are taking, and ask the pharmacist to check for drug interactions before starting any new drugs
- Report any conditions that may affect their electrolyte levels (e.g., diarrhea, vomiting, renal dysfunction)

References:

1. QT interval and drug therapy. Drug and Therapeutics Bulletin. BMJ 2016; 353:i2732
2. Virani, SA, Dent S, et al. Canadian Cardiovascular Society Guidelines for Evaluation and Management of Cardiovascular Complications of Cancer Therapy. Canadian Journal of Cardiology 2016; Volume 32, Issue 7, 831 - 841
3. http://www.uptodate.com/contents/acquired-long-qt-syndrome, Accessed Jun.8.2016
4. Drug-induced QT prolongation and Torsades de Pointes - the facts. New Zealand Ministry of Health. Prescriber Update 31(4): 27-29,December 2010.
5. Kannankeril P, Roden DM, Darbar D. Drug-Induced Long QT Syndrome. Sibley D, ed. Pharmacological Reviews. 2010;62(4):760-781. doi:10.1124/pr.110.003723.
6. Drew BJ, Ackerman MJ, Funk M, et al. Prevention of Torsade de Pointes in Hospital Settings: A Scientific Statement From the American Heart Association and the American College of Cardiology Foundation. Journal of the American College of Cardiology. 2010;55(9):934-947. doi:10.1016/j.jacc.2010.01.001
7. Keating NL, O'Malley AJ, Smith MR. Diabetes and cardiovascular disease during androgen deprivation therapy for prostate cancer. J Clin Oncol. 2006;24:4448–4456.
8. Yee Guan Yap, A John Camm. Drug Induced http://heart.bmj.com/content/89/11/1363.fullQT Prolongation and torsades de pointes. Education in Heart. Heart 2003;89:1363-1372 doi:10.1136/heart.89.11.1363
9. Al-Khatib SM, LaPointe N, Kramer JM, Califf RM. What Clinicians Should Know About the QT Interval. JAMA. 2003;289(16):2120-2127. doi:10.1001/jama.289.16.2120
10.. de Lemos M, Kung C, Kletas V, Badry N, Kang I. Approach to initiating QT-prolonging oncology drugs in the ambulatory setting. J Oncol Pharm Pract. Jan 2018

Reviewed: January 16, 2018