Clinical Pharmacology & Toxicology Pearl of the Week

~Drug-Induced Prolonged QTc ~

✓ What are the QT and QTc intervals?

- ✓ The QT interval is measured from an electrocardiogram (ECG) from the start of the Q wave to the end of the T wave or predicted intersection of the T wave downslope and the baseline.
- ✓ The QT interval corresponds to the time taken for ventricular depolarisation and repolarization.
- ✓ The QT interval changes with heart rate. Therefore, a corrected QT interval (QTc) is often used to allow for assessment of interval length independent of heart rate.
- ✓ QTc can be calculated by many formulas such as the Bazett, Fridericia, Framingham Linear Regression, and Rautaharju Formulae. Ex: Bazett: QTc = $QT/\sqrt{R-R\ interval}$
- ✓ Prolonged QTc is defined as a QTc >440ms in men or a QTc >460ms in women.[1]

✓ Why is QTc prolongation dangerous?

- ✓ QTc >500ms is an independent risk factor for developing Torsades des Pointes (TdP). [1]
- ✓ For acute ingestions with QTc prolonging drugs, it has been suggested that the absolute QT interval (not QTc) is a better predictor of the risk of TdP. [1]
  - Values can be plotted on the QT interval nomogram (Figure 1) to evaluate for risk of TdP.[2]

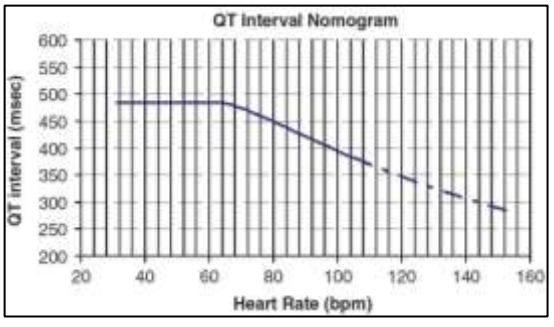

Figure 1. Upper Limit of Normal (95 percentile) of absolute QT vs Heart rate.[2]

✓ Mechanism of QTc prolongation on ECG

- ✓ QTc prolongation occurs when phase 2 or 3 of the action potential is prolonged (Figure 2).
- ✓ Generally, slow potassium efflux due to potassium channel dysfunction prolongs the repolarization phases 2 and 3. This can be due to delayed rectifier potassium channel blockade, hypokalemia, and hypomagnesemia (causing intracellular hypokalemia).
- ✓ Additional mechanisms of prolonged QTc include hypocalcaemia slowing phase 2 of the action potential, as well as sodium channel blockade resulting in prolonged QRS (and resultant prolonged QTc).

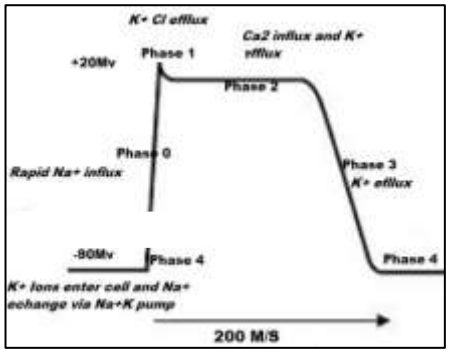

Figure 2. Phases of the cardiac action potential and associated ion channels involved.[7]

✓ Mechanism of drug induced QTc prolongation

- ✓ In drug induced QTc prolongation, prolongation results due to blockade of the hERG delayed potassium rectifier channel.[3]
- ✓ This channel plays a key role in phase 3 of the cardiac action potential, where repolarization occurs.
- ✓ The hERG delayed potassium rectifier channel contains a relatively large pore size with multiple hydrophobic pockets allowing for promiscuous binding of a wide range of xenobiotics within the channel. This accounts for the long list of medication implicated in prolonging the QTc interval.[4]

✓ Drugs causing QTc prolongation

- ✓ Many commonly used medications are associated with QTc prolongation including antiarrhythmics, antibiotics, antidepressants, anti-emetics, antihistamines, and antimalarials.
- ✓ A list of commonly used medications that cause QTc prolongation is included in Table 1.

Class of Drug	Examples
Antiarrhythmic	Amiodarone, Procainamide, Quinidine, Sotalol
Antipsychotics	Chlorpromazine, Clozapine, Haloperidol, Quetiapine, Risperidone
Antibiotics	Azithromycin, Clarithromycin, Erythromycin, Fluconozaole, Ketoconazole, Ciprofloxacin, Levofloxacin, Moxifloxacin, Trimethroprim-Sulfamethoxazole
Antidepressants	Amitriptyline, Citalopram, Fluoxetine, Nortriptyline, Paroxetine, Sertraline, Venlafaxine
Anti-emetics	Ondansetron, Prochlorperazine

Table 1. Examples of commonly used medications associated with prolonged QTc. (Adapted from Ayad et al. 2010).[6]

- ✓ **Are all QTc prolonging drugs equally likely to cause Tdp?**
  - ✓ Although many drugs are known to cause prolonged QTc, some drugs are more commonly reported to cause TdP.[5] Examples can be found in Table 2.
  - ✓ Visit http://crediblemeds.org or download the app Credmeds for a searchable database of drugs for risk of QTc prolongation and TdP.

Class of Drug	Examples
Antiarrythmics	Amiodarone, Procainamide, Quinidine, Sotalol
Antibiotics	Clarithromycin, Erythromycin
Antipsychotic agents	Chlorpromazine, Haloperidol,
Anti-emetics	Domperidone, Droperidol
Opioids	Methadone
Others	Arsenic trioxide, Cisapride

Table 2. Examples of drugs that may cause TdP, secondary to long QTc. (Adapted from Roden, DM. 2004).[5]

- ✓ **Treatment of a prolonged QTc**
  - ✓ Identify and remove drugs associated with prolonged QTc from patient's profile.
  - ✓ Avoid the use of other QTc prolonging medications.
  - ✓ Identify and correct electrolyte abnormalities; particularly hypokalemia, hypocalcaemia and hypomagnesemia.
  - ✓ Monitor for arrhythmias. If TdP develops, treat per ACLS guidelines. Consider magnesium sulphate empirically if serum magnesium concentration unknown. Consider continuous cardiac monitoring if QTc >500 ms. Consider serial ECGs every two to six hours until resolution.

References:

1. Bruns E. QTC Interval. Life in the Fast Lane [Internet]. 2019 May 1 [Cited 2019 September 30]. Available from: https://litfl.com/QTc-interval-ecg-library/
2. Isbister GK. Risk assessment of drug-induced QTC prolongation. Australian prescriber. 2015;38(1):20.
3. Nachimuthu S, Assar MD, Schussler JM. Drug-induced QTC interval prolongation: mechanisms and clinical management. Ther Adv Drug Saf. 2012 Oct; 3(5): 241-253.
4. Vandenberg JI, Perozo E & Allen TW. Towards a structural view of drug binding to hERG K^+ channels. Trends Pharmacol Sci. 2017; 38:899–907.
5. Roden D. Drug-Induced Prolongation of the QTC Interval. N Engl J Med. 2004; 350:1013-1022.
6. Ayad RF, Assas MD, Simpson L, Garner JB, Schussler JM. Causes and management of drug-induced long QTC syndrome. Proc (Bayl Univ Med Cent). 2010 Jul; 23(3):250-255.
7. Emergency Medical Paramedic [Internet]. [Cited 2019 October 2]. Available from http://www.emergencymedicalparamedic.com/cardiac-action-potential/

The Calgary Clinical Pharmacology physician consultation service is available Mon-Fri, 9am-5pm. The on-call physician is listed in ROCA. Click HERE for clinical issues the CP service can assist with.

The Poison and Drug Information Service (PADIS) is available 24/7 for questions related to poisonings. Please call 1-800-332-1414, and select option 1.