Minimizing Drug-Induced QT Interval Prolongation in Critical Care Cardiac Patients

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Agenda

- QTc prolongation and Torsades de pointes (TdP)

- Risk factors inducing QTc prolongation and Torsades de pointes (TdP)

- Role of clinical pharmacist in reducing the risk of drug-induced QTc prolongation and Torsades de pointes (TdP)

- Evidence from literature.
ECG (QTc prolongation & Torsades de pointes (TdP))

Normal ECG

QT Interval Prolongation

Torsade de Pointes
Corrected QT (QTc)

The normal QTc interval in adults:

- 0.36 to 0.47 s (360–470 ms) in men
- 0.36 to 0.48 s (360–480 ms) in women

**Bezett's Formula**

\[ QTc = \frac{QT \text{ interval}}{\sqrt{RR}} \]

**QTc** = Corrected QT interval
**QT interval** = Q wave to end of T wave
**RR** = Time from two consecutive R waves

**Example Calculation**

\[ QTc = \frac{QT}{\sqrt{RR(s)}} = \frac{0.32}{\sqrt{0.6}} = 0.41 \text{ s} \]

Clinically significant QT prolongation, usually defined as

- >500 ms or >60 to 70 ms change from baseline

J Am Coll Cardiol. 2010; 55:934–947
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Risk factors inducing QTc prolongation and TdP

Patient related risk factors

Drugs related risk factors
Patient related risk factors

1- QTc interval >500 ms

2- Possible Genetic Predisposition

3- Advanced Age

Can Pharm J (Ott). 2016 May; 149(3): 139–152
5- Acute Myocardial Infarction
6- Acute Myocardial Infarction
7- Heart Failure

Inadequate dose adjustment of renally eliminated QT prolonging drug(s) in patients with renal impairment

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Drugs induced QT prolongation categorization

- **Known Risk**
  - Drugs prolong the QT interval and TdP even when taken as directed in official labeling.

- **Possible Risk**
  - Can prolong QT interval but there is insufficient evidence at when used as directed in official labeling, are associated with a risk of causing TdP.

- **Conditional Risk**
  - Risk of TdP but only under certain conditions (e.g., excessive dose, hypokalemia, congenital LQTS or by causing a drug-drug interaction that results in excessive QT interval prolongation).

**Drugs to Avoid in Congenital Long QT**

Drugs on this list include those in the above 3 risk categories and other drugs that do not prolong the QT interval per se but have a theoretical risk of causing arrhythmia that is based on their known stimulant actions on the heart.
Drugs of Known Risk

- Propofol & Sevoflurane
- Fluconazole & Pentamidine
- Ondansetron & Domperidone
- Amiodarone, Disopyramide, Dofetilide, Flecaainide, Ibutilide, Procainamide, Quinidine and Sotalol
- Citalopram & Escitalopram
- Haloperidol, Chlorpromazine, Pimozide and Thioridazine
- Methadone, Cilostazol, Terlipresin and Donepezil
Over the past 20 years, several drugs, have been withdrawn from the market as a result of causing deaths due to TdP.

- Astemizole
- Terfenadine
- Cisapride
- Grepafloxacin
Drug-Drug interactions associated with QTc interval prolongation and torsades de pointes

May be
* pharmacodynamic interactions: concomitant drugs prolong QT interval.
* pharmacokinetic interactions: inhibit enzymes responsible for the metabolism of drug inducing QT prolongation.

Inhibition of CYP 3A4

Amiodarone
Disopyramide
Dofetilide
Pimozide

Can Pharm J (Ott). 2016 May; 149(3): 139–152
Drugs known to cause QT Interval prolongation torsades de pointes that require dose adjustment in patients with **acute kidney injury or chronic kidney disease**

- Ciprofloxacin
- Disopyramide
- Dofetilide
- Flecainide
- Fluconazole
- Levofloxacin
- Procainamide
- Sotalol
How to Minimize drug-induced QT interval prolongation in critical care cardiac patients

Identification of patients at risk

Identifying Drugs inducing QT interval prolongation

CardioEgypt2017
Clinical Pharmacist QTc Interval monitoring worksheet

Patient Name: __________ Age: _______ weight: ______ Diagnosis: _______________________

Drug Suspected to induce QTc Prolongation: __________________________________________

Drug Indication: ________________________________________________________________

Dose: ___________________ Expected Duration of use: ______________________________

History of drug-induced torsades de pointes:

☐ Yes          ☐ No

History of previous sudden cardiac arrest:

☐ Yes          ☐ No

History of congenital long QT syndromes:

☐ Yes          ☐ No
**QT interval prolongation risk score:**

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥68 years</td>
<td>1</td>
</tr>
<tr>
<td>Female</td>
<td>1</td>
</tr>
<tr>
<td>Loop diuretic</td>
<td>1</td>
</tr>
<tr>
<td>Serum potassium ≤3.5 mmol/L</td>
<td>2</td>
</tr>
<tr>
<td>Presenting QT_c interval ≥450 ms</td>
<td>2</td>
</tr>
<tr>
<td>Acute myocardial infarction†</td>
<td>2</td>
</tr>
<tr>
<td>Heart failure with reduced ejection fraction</td>
<td>3</td>
</tr>
<tr>
<td>1 QT_c interval-prolonging drug‡</td>
<td>3</td>
</tr>
<tr>
<td>≥2 QT_c interval-prolonging drugs‡</td>
<td>3</td>
</tr>
<tr>
<td>Sepsis†</td>
<td>3</td>
</tr>
<tr>
<td>Maximum score</td>
<td>21</td>
</tr>
</tbody>
</table>

**Score:**

- **< 7 Low Risk** (no need for baseline ECG unless additional risk factors develop or if a drug interaction is likely)
- **7-10 Moderate Risk** (ECG required)
- **≥ 11 High Risk** (ECG required)

*Circ Cardiovasc Qual Outcomes 2013;6:479-87*

Ng TM, Ball AM, Hara JM, Touchette DR, Dansky KN, Lindsay TT, Puurnala SE.

Abstract

BACKGROUND: No data exist regarding the value of pharmacist monitoring of drugs associated with QTc interval prolongation.

OBJECTIVE: To assess the capability, clinical impact, and economic impact of pharmacists monitoring for drug-induced QTc interval prolongation in critically ill medical adult patients.

METHODS: In a prospective, parallel-group study, 149 consecutive medical intensive care unit (ICU) patients prescribed a QTc interval-prolonging drug at the Los Angeles County + University of Southern California Medical Center were assigned on alternating days to an intervention group (clinical pharmacist on physician team monitored drugs using a standardized algorithm) or a standard care group (team without pharmacist using an algorithm). The monitoring algorithm used daily assessments of electrocardiograms and laboratory data to generate pharmacotherapeutic recommendations. The primary endpoint was the frequency of QTc interval prolongation (>600 msec at any time or an increase > or =60 msec over baseline). Secondary endpoints included QTc interval greater than 470 msec in women or greater than 450 msec in men, mean increase in QTc interval at 48 hours, recommendation acceptance rate, and cost of care.

RESULTS: QTc interval prolongation occurred less frequently in the intervention group compared with the standard care group (19% vs 39%, respectively; p = 0.006). Incidence of QTc interval greater than 500 msec (13% vs 33%, respectively; p = 0.003) was also lower in the intervention group. Incidence of QTc interval increase of 60 msec or more over baseline (12% vs 21%, respectively; p = 0.12) and increase in QTc interval at 48 hours over baseline (mean +/− SD: 6.4 +/− 40.8 vs 18.2 +/− 42.3 msec, respectively; p = 0.097) were not significantly different between the groups. Algorithm-generated recommendations were accepted 70% of the time by the intervention group physician team. Total cost and cost per day were not significantly different between groups.

CONCLUSIONS: In this preliminary study, pharmacist monitoring of QTc interval-prolonging drugs using a simple algorithm was feasible and reduced the risk of QTc interval prolongation. Further studies that monitor other proarrhythmic medications are warranted.
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Evidence from literature

An 83-year-old female known patient of heart failure controlled on Captopril 50 mg tid, Concor 5 mg once daily and furosemide 40 mg twice daily was hospitalized in the intensive care unit for pneumonia. She was started on intravenous erythromycin several hours before cardiac arrest (Due to Torsades de Pointes). One Hour before arrest: ECG 1 hour before the onset of TdP shows extreme prolongation of the QT interval (730 ms) and macroscopic T-wave alternans (vertical arrows). If these signs of impending TdP had been recognized, discontinuation of the culprit drug and administration of magnesium most likely would have prevented the subsequent cardiac arrest.
Take Home Message

- QTC prolongation and Torsades de pointes can be catastrophic event and lead to cardiac arrest.

- Clinical pharmacist can help medical team in identifying and reducing Risk factors inducing QTC prolongation and Torsades de pointes

- Clinical pharmacist can help medical team in excluding other causes of QTC prolongation and Torsades de pointes before discontinuing the culprit drug.

- Early recognition, of the culprit drug and proper management most likely will prevent cardiac arrest.
References


• Tisdale JE. Drug-induced QT interval prolongation and torsades de pointes: Role of the pharmacist in risk assessment, prevention and management. Can Pharm J (Ott). 2016;149(3):139-52


