Drug-induced QTc Prolongation

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April 25, 2020

Financial Disclosures

- None

Objectives

- Identify risk factors for prolonged QT interval in patient case
- Utilize a risk score calculator to categorize patient risk for QT interval prolongation
- Describe monitoring recommendations for patients at risk for QT interval prolongation

Patient Case 1

BC is an 69 year old female admitted to your hospital for CAP. You enter an order for levofloxacin 750 mg daily and get a warning about QT prolongation.

Current med list:
- Citalopram 20mg daily
- Hydrochlorothiazide 25 mg daily
- Lisinopril 20 mg daily
- Apixaban 5 mg BID
- Metoprolol succinate 50 mg daily

Poll Question 1 (mark all that apply)

Which medication(s) on her list are involved in this interaction?

- Citalopram
- Hydrochlorothiazide
- Lisinopril
- Apixaban
- Metoprolol succinate
- None are involved

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

Li M, et al. P&T Community 2017, 242(7):473-477

CredibleMeds

AVAILABLE TDP RISK CATEGORIES
You can select multiple categories.

⚠️ Known Risk of TdP — *Definition of this Category*

❓ Possible Risk of TdP — *Definition of this Category*

🔵 Conditional Risk of TdP — *Definition of this Category*

⬛ Drugs to Avoid in Congenital Long QT — *Definition of this Category*

⚠️ These drugs prolong the QT interval AND are clearly associated with a known risk of TdP, even when taken as recommended

❓ These drugs can cause QT prolongation BUT currently lack evidence for a risk of TdP when taken as recommended

⬛ These drugs pose a high risk of TdP for patients with CLQTS

🔵 These drugs are associated with TdP BUT only under certain conditions

Generic Name(s)	Levofloxacin
Brand Names (Partial List)	Levaquin, Tavanic
Current TdP risk category	⚠️ Drugs with known TdP risk ❌ Drugs to be avoided by congenital Long QT
Main Therapeutic Use(s)	Bacterial infection
Route(s) administered	oral, injection
Market Status	On US and non US Market
Info in Drug Label	
QT increase mentioned	Yes
TdP cases mentioned	Yes
ECG Recommendations	No ECG recommendation
Warning for use in patients with congenital LQTS	Caution
Contraindicated Concomitant medicines:	None

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LEXICOMP

Title Quinolones / Angiotensin-Converting Enzyme Inhibitors

Print

Risk Rating B: No action needed

Summary Angiotensin-Converting Enzyme Inhibitors may enhance the arrhythmogenic effect of Quinolones. Quinolones may enhance the nephrotoxic effect of Angiotensin-Converting Enzyme Inhibitors.
Severity Moderate **Reliability Rating** Good

Patient Management No action needed. If ACE inhibitors and fluoroquinolones are used concomitantly in patients with other risk factors for either acute kidney injury or arrhythmias, more frequent monitoring of renal function or cardiac rhythm may be appropriate.

Drug-Drug Interactions

Pharmacodynamics

↑ Concomitant use of two drugs that prolong the QT interval will <u>increase the risk</u> of QT prolongation and TdP

Pharmacokinetics

↑ Changes in metabolism or excretion of medications that can <u>increase the risk</u> of QT prolongation and TdP

Poll Answer 1

Which medication(s) on her list are involved in this interaction?

- Citalopram
- Hydrochlorothiazide
- Lisinopril - maybe
- Apixaban
- Metoprolol succinate
- None are involved

Type answers in the Chat box

Back to the case:

Before continuing with the order, what other information do you want to know about this patient?

PMH

- HFrEF
- Hypertension
- Afib
- Depression

OTC meds

Poll Question 2

- Which of the following over-the-counter meds has not been associated with QTc prolongation?
  - Loperamide
  - Acetaminophen
  - Famotidine
  - Omeprazole
  - Diphenhydramine

	Risk Category	Conditions for TdP
Loperamide	conditional risk	-Excessive dose -Impaired drug elimination
Diphenhydramine	conditional risk	-Excessive dose
Famotidine	conditional risk	-Low serum K or Mg -Excessive dose -Impaired drug elimination -Concomitant QT/TdP meds
Omeprazole	conditional risk	-Concomitant QT/TdP meds -Can cause low serum K or Mg

Poll Answer 2

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  - Famotidine
  - Omeprazole
  - Diphenhydramine

Case OTC meds

- Acetaminophen 500 mg – as needed
- Multi vitamin- daily

Case Vitals/Labs/EKG

- HR: 85 bpm
- K: 3.0 mmol/L
- Mg: 2.0 mg/dL
- Ca: 9.4 mg/dL
- SCr: 0.8 mg/dL (CrCl = 75 mL/min)
- QTc Int: 446 ms

Poll Question 3 (mark all that apply)

Which of the following abnormal values are risk factors for prolonged QT interval for this patient?

- HR: 85 bpm
- K: 3.0 mmol/L
- Mg: 2.0 mg/dL
- Ca: 9.4 mg/dL
- SCr: 0.8 mg/dL (CrCl = 75 mL/min)
- QTc Int: 446 ms

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What is a "normal" QT?

- QT_c > 450 ms in men and QT_c > 470 ms in women were associated with an increased risk of sudden death

- Another study states normal: 440 ms in men and 460 ms in women

- Multiple references: QT_c greater than 500 ms is often regarded as a significant risk of TdP

Straus DM, et al. J Am Coll Cardiol 2006; 47:362-367
Molnar J, et al. J Am Copll Cardiol 1996; 27:76-83
Roden DM, et al. N Engl J Med. 2004; 350:1013-1022

Type answers in the chat box

What are some other risk factors this patient has for QT prolongation/TdP?

Risk Factors

- Age (>65 years)
- Bradycardia
- Congenital long QT syndrome
- Diuretics
- Electrolyte disturbances
- Gender (female)
- Heart disease
- Baseline or new onset QTc> 500 ms
- Increase in QTc of > 60 ms
- Medications
  - More than one QT prolonging medication
  - Rapid infusion of QT prolonging med
  - Drug dose
  - Drug interactions
  - Inappropriately dosed QT meds (renal or hepatic impairment)
- Recent cardioversion

Drew BJ, et al. Circulation 2010; 121:1017-1060

Case Risk Factors

Age > 65

Diuretic

Hypokalemia

Female

HFrEF

Other QT meds

Are any modifiable?

Poll Question 4

- Which of the following is used to help identify those at risk for QTc interval prolongation?
  - ASCVD Risk Calculator
  - CHA_2DS_2VASc Score
  - Tisdale Risk Score
  - TIMI Risk Score
  - Centor Score

Can we predict this?

- Tisdale Risk Score
  - Identifies patients at risk for QT_c interval prolongation
  - Odds ratio to develop scoring system
    - OR of 1.3 = 1 point
    - OR of 2.1 = 2 points
    - OR of 2.8 = 3 points

Tisdale JE, et al. Circ Cardiovasc Qual Outcomes 2013; 6:479-487

Tisdale Risk Score

Risk Factor	Points
Age ≥ 68 years	1
Female sex	1
Loop diuretic	1
Serum K$^+$ ≤ 3.5 mEq/L	2
Admission QTc ≥ 450 ms	2
Acute MI	2
≥ 2 QTc-prolonging drugs	3
Sepsis	3
Heart failure	3
One QTc-prolonging drug	3
Maximum Risk Score	**21**

K$^+$ = potassium
MI = Myocardial infarction

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Tisdale Risk Score

Risk Category	Score	Incidence	Sensitivity	Specificity	PPV	NPV
Low (n=159)	≤ 6	15 %	NR	NR	NR	NR
Moderate (n=101)	7-10	37%	67%	88%	79%	88%
High (n=40)	≥ 11	73%	74%	77%	79%	76%

PPV = positive predictive value
NPV = negative predictive value
NR = not reported

Tisdale JE, et al. Circ Cardiovasc Qual Outcomes 2013; 6:479-487

Case Tisdale Risk Score

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Poll Question 5

- In general when should the QTc be monitored?

    – 30 minutes after medication initiation

    – 8 hours after medication initiation

    – Only if an overdose is suspected

    – Only if symptoms occur

Monitoring

AHA/ACC suggests the following:

- Document the QTc interval
  - Before medication administration
  - At least every 8 to 12 hours after the initiation, increased dose, or overdose of QT-prolonging drugs
- If QTc prolongation is observed, more frequent measurements should be documented

Drew BJ, et al. J Am Coll Cardiol 2010; 55(9):934-947

Monitoring

Credible Meds

- If possible, do not initiate QT-prolonging drugs
  - Female: QT>440ms
  - Male: QT>420ms
- During treatment, do not allow the QT >500ms

Poll Answer 5

- In general when should the QTc be monitored?

  - 30 minutes after medication initiation
  - 8 hours after medication initiation
  - Only if an overdose is suspected
  - Only if symptoms occur

Managing QTc prolongation

- Discontinue contributing agents
- Find alternate therapy
- Assess and address electrolyte abnormalities
- Have external defibrillator ready

Tips for preventing drug induced QTc prolongation

- Obtain baseline and routine ECGs on at risk patients and monitor QTc
- Be attentive to electrolyte disturbances (especially in high risk patients)
- Assess for drug interactions
- Renally/hepatically adjust medication doses when necessary

REPORTING ADVERSE DRUG REACTIONS

MedWatch at 1-888-INFO-FDA

www.fda.gov/Safety/Medwatch/How-ToReport/ucm085568.htm.

Other Medications of Interest

	Risk Category	Recommendations
Chloroquine	⚠️ ❌ CLQT known risk	Monitor ECG
Hydroxychloroquine	⚠️ ❌ CLQT known risk	Monitor QT during use
Azithromycin	⚠️ ❌ CLQT known risk	No ECG recommendation
Lopinavir/ritonavir	❓ ❌ CLQT possible risk	No ECG recommendation

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