Antiarrhythmics & QT Prolongation: Avoiding Drug Interactions

MELINDA DEUBNER, PHARMD, BCCCP

A webinar for HealthTrust members
August 24, 2018
Disclosures

- The presenter has no real or perceived conflicts of interest related to this presentation.
- This program contains the mention of suppliers, brands, products, services or drugs presented in a case study or comparative format using evidence-based research. Such examples are intended for educational and informational purposes and should not be perceived as an endorsement of any particular supplier, brand, product, service or drug.
Learning Objectives

1. Describe the electrophysiology of the heart and the connection between different ion channels and the electrocardiogram.
2. Identify antiarrhythmic classes and their effects on the QT interval.
3. Manage interactions between antiarrhythmic medications and other drugs which may cause QT prolongation.
Drug Induced QT Prolongation

True prevalence difficult to assess

Arrhythmias typically fatal outside the hospital

Many patients exposed to QT-prolonging agents in ICU

Increased drastically in cardiovascular ICU

ICU patients at high risk for drug-drug interactions

18.6% of patients on >1 QT-prolonging drug had increased mortality

Cardiac Action Potential

Action Potential & the ECG

QT Prolongation

Caused by blocking of potassium efflux leading to delayed ventricular repolarization

Normal QT interval in is <440 msec* in men, <450 msec in women

Puts patient at risk for reentry arrhythmias, particularly Torsades de Pointes (TdP)

TdP is generally associated with a QT interval > 500 msec


*msec = Millisecond
Torsades de Pointes

Can lead to sudden cardiac death

Treatment:

- Direct cardioversion for episodes longer than 5 seconds
- Immediate defibrillation if pulseless
- Magnesium 2g slow IV push

Poll: Test Your Understanding

Which ion channels would need to be affected to cause QT prolongation?

A. Sodium channels
B. Potassium channels
C. Calcium channels
D. All of the above
Which ion channels would need to be affected to cause QT prolongation?

A. Sodium channels
B. Potassium channels
C. Calcium channels
D. All of the above
## Antiarrhythmic Drug Actions

Antagonist relative potency:
- L = Low
- M = Moderate
- H = High

ACh = Acetylcholine
Ado = Adenosine

### Table: Antiarrhythmic Drug Actions

<table>
<thead>
<tr>
<th>Vaughan-Williams Class</th>
<th>DRUG</th>
<th>ECG Changes</th>
<th>CHANNELS</th>
<th>RECEPTORS</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Quinidine</td>
<td>A</td>
<td>M</td>
<td>L</td>
</tr>
<tr>
<td></td>
<td>Procainamide</td>
<td></td>
<td>M</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Disopyramide</td>
<td></td>
<td>M</td>
<td></td>
</tr>
<tr>
<td>IB</td>
<td>Lidocaine</td>
<td>B</td>
<td>L</td>
<td>M</td>
</tr>
<tr>
<td></td>
<td>Mexiletine</td>
<td></td>
<td>M</td>
<td></td>
</tr>
<tr>
<td>IC</td>
<td>Propafenone</td>
<td>C</td>
<td>H</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Flecaïnide</td>
<td></td>
<td>M</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>β-Adrenergic antagonists</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dronedarone</td>
<td></td>
<td>L</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Amiodarone</td>
<td></td>
<td>L</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sotalol</td>
<td></td>
<td>L</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ibutilide</td>
<td></td>
<td>L</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dofetilide</td>
<td></td>
<td>L</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>Verapamil</td>
<td></td>
<td>M</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diltiazem</td>
<td></td>
<td>M</td>
<td></td>
</tr>
<tr>
<td>Misc</td>
<td>Adenosine</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Legend:**
- △ = Agonist
- = ECG Changes related to Ca^{2+} channel block
- = ECG Changes related to Na^{+} channel block
- = ECG Changes related to K^{+} channel block

## Class Ia Antiarrhythmics

### Agents: Quinidine, Procainamide, Disopyramide

<table>
<thead>
<tr>
<th>Mechanism of Action</th>
<th>Indication</th>
<th>Arrhythmia</th>
</tr>
</thead>
</table>
| • Moderately blocks sodium influx and potassium efflux | • Atrial fibrillation and flutter  
• Ventricular and supraventricular tachyarrhythmias | • Prolonged QT interval  
• May cause Torsades de Pointes |

## Class Ia Antiarrhythmics

<table>
<thead>
<tr>
<th></th>
<th><strong>Quinidine</strong></th>
<th><strong>Procainamide</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Usual Dose Range</strong></td>
<td>200-600mg PO Q 6-12 hours</td>
<td>Max total IV dose of 100mg (as boluses or infusion)</td>
</tr>
<tr>
<td><strong>Kinetics</strong></td>
<td>Metabolized by CYP3A4</td>
<td>Metabolized by CYP2D6</td>
</tr>
<tr>
<td><strong>Risk of QT Prolongation</strong></td>
<td>High</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

# Class Ib Antiarrhythmics

## Mechanism of Action
- Weakly blocks sodium channels

## Indication
- Ventricular arrhythmias

## Arrhythmia
- Not associated with negative affects on cardiac rhythm
- Shorten QT interval

### Agents: Lidocaine, Mexilitine

# Class Ib Antiarrhythmics

<table>
<thead>
<tr>
<th></th>
<th>Lidocaine</th>
<th>Mexilitine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Usual Dose Range</strong></td>
<td>1-1.5mg/kg IV bolus, with max cumulative dose of 3mg/kg</td>
<td>150-300 mg PO Q 8-12 hours</td>
</tr>
<tr>
<td><strong>Kinetics</strong></td>
<td>Metabolized by CYP3A4</td>
<td>Metabolized by CYP2D6</td>
</tr>
<tr>
<td><strong>Risk of QT Prolongation</strong></td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

Class Ic Antiarrhythmics

Agents: Propafenone, Flecainide

Mechanism of Action
- Highly blocks sodium influx

Indication
- Ventricular and supraventricular tachyarrhythmias

Arrhythmia
- Can prolong QT
- Ischemia predisposes patients to reentry tachyarrhythmias
- Avoid in patients with CAD

### Class Ic Antiarrhythmics

<table>
<thead>
<tr>
<th></th>
<th>Propafenone</th>
<th>Flecainide</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Usual Dose Range</strong></td>
<td>150-300mg PO Q 8 hours</td>
<td>50-200mg PO Q 12 hours</td>
</tr>
<tr>
<td><strong>Kinetics</strong></td>
<td>Metabolized by CYP2D6</td>
<td>Metabolized by CYP2D6</td>
</tr>
<tr>
<td><strong>Risk of QT Prolongation</strong></td>
<td>Low Risk (higher in patients with CAD)</td>
<td>Low Risk (higher in patients with CAD)</td>
</tr>
</tbody>
</table>

# Class II Antiarrhythmics

## Mechanism of Action
- Blocks beta adrenergic receptors

## Indication
- Hypertension, angina, MI, heart failure (varies by agent)

## Arrhythmia
- Low risk
- May cause some AV block

---

**Agents:** Metoprolol, Labetalol, Esmolol, etc.

**Sources:**
- Woosley RL. CredibleMeds. QTdrugs List. [https://crediblemeds.org/new-drug-list/](https://crediblemeds.org/new-drug-list/).
## Class II Antiarrhythmics

<table>
<thead>
<tr>
<th>Usual Dose Range</th>
<th>Metoprolol</th>
<th>Labetalol</th>
<th>Esmolol</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Usual Dose Range</strong></td>
<td>25-200mg PO Q 12-24 hours</td>
<td>10-80mg IV Q 20 min (max 300mg/day)</td>
<td>500-1000mcg/kg IV bolus, then 50-300 mcg/kg/min</td>
</tr>
<tr>
<td><strong>Kinetics</strong></td>
<td>Metabolized by CYP2D6</td>
<td>Metabolized by glucuronide conjugation</td>
<td>Metabolized by red blood cell esterases</td>
</tr>
<tr>
<td><strong>Risk of QT Prolongation</strong></td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

# Class III Antiarrhythmics

**Agents:** Amiodarone, Dofetilide, Sotalol, Dronedarone, etc.

<table>
<thead>
<tr>
<th>Mechanism of Action</th>
<th>Indication</th>
<th>Arrhythmia</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Highly block potassium channels</td>
<td>• Atrial and ventricular tachyarrhythmias</td>
<td>• Low to high risk depending on agent</td>
</tr>
<tr>
<td>• Can also have affects on Na and Ca channels as well as adrenergic receptors</td>
<td></td>
<td>• QT prolongation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• May cause Torsades de Pointes</td>
</tr>
</tbody>
</table>

# Class III Antiarrhythmics

<table>
<thead>
<tr>
<th></th>
<th>Amiodarone</th>
<th>Dofetilide</th>
<th>Sotalol</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Usual Dose Range</strong></td>
<td>200-400mg PO Q 8-24 hours</td>
<td>250-500mcg PO Q 12 hours</td>
<td>80-160mg PO Q 12 hours</td>
</tr>
<tr>
<td><strong>Kinetics</strong></td>
<td>Metabolized by CYP3A4 and CYP2C8</td>
<td>Metabolized by CYP3A4</td>
<td>Excreted in urine as unchanged drug</td>
</tr>
<tr>
<td><strong>Risk of QT Prolongation</strong></td>
<td>Low</td>
<td>High</td>
<td>High</td>
</tr>
</tbody>
</table>

Class IV Antiarrhythmics

**Agents: Verapamil, Diltiazem**

<table>
<thead>
<tr>
<th>Mechanism of Action</th>
<th>Indication</th>
<th>Arrhythmia</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Moderately blocks calcium channels</td>
<td>• Atrial fibrillation, supraventricular tachycardias, hypertension, angina</td>
<td>• Low risk</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• May cause some AV block</td>
</tr>
</tbody>
</table>

### Class IV Antiarrhythmics

<table>
<thead>
<tr>
<th></th>
<th>Verapamil</th>
<th>Diltiazem</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Usual Dose Range</strong></td>
<td>80-160mg PO Q 8 hours</td>
<td>15-20mg IV, then 5-15 mg/hour</td>
</tr>
<tr>
<td><strong>Kinetics</strong></td>
<td>Metabolized by CYP3A4</td>
<td>Metabolized by CYP3A4</td>
</tr>
<tr>
<td><strong>Risk of QT Prolongation</strong></td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

Antiarrhythmics and QT Prolongation

May Prolong QT

- Class Ic (Propafenone, Flecainide)

Associated with TdP

- Class Ia (Quinidine, Procainamide, Disopyramide)
- Class III (Amiodarone, Dofetilide, Sotalol, Dronedarone, Ibutilide)

Other Risk Factors for Drug-induced Arrhythmias

- Preexisting cardiac disease
- Shock and vasopressor use
- Organ failure and impaired kinetics
- Electrolyte imbalances
- Drug-drug interactions

Electrolyte Imbalances

- Hypo/Hyperkalemia
- Hypomagnesemia
- Hypocalcemia

Poll: Test Your Understanding

Which one of these drugs could cause an arrhythmia through electrolyte disturbances?

A. Nitrofurantoin
B. Acetaminophen
C. Ceftriaxone
D. Albuterol
Which one of these drugs could cause an arrhythmia through electrolyte disturbances?

A. Nitrofurantoin
B. Acetaminophen
C. Ceftriaxone
D. Albuterol
# Drugs Causing Electrolyte Imbalances

<table>
<thead>
<tr>
<th>Hypokalemia</th>
<th>Hypomagnesemia</th>
<th>Hyperkalemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Beta agonists</td>
<td>- Diuretics (loop and thiazide)</td>
<td>- Potassium-sparing diuretics</td>
</tr>
<tr>
<td>- Catecholamines</td>
<td>- Aminoglycosides</td>
<td>- ACE inhibitors</td>
</tr>
<tr>
<td>- Insulin</td>
<td>- Amphotericin B</td>
<td>- NSAIDs</td>
</tr>
<tr>
<td>- Diuretics (loop and thiazide)</td>
<td>- Cisplatin</td>
<td>- Succinylcholine</td>
</tr>
<tr>
<td>- Aminoglycosides</td>
<td>- Cyclosporine</td>
<td>- Beta antagonists</td>
</tr>
<tr>
<td>- Amphotericin B</td>
<td>- Digoxin</td>
<td>- Digoxin</td>
</tr>
<tr>
<td>- Steroids</td>
<td>- Mannitol</td>
<td>- SMX/TMP</td>
</tr>
</tbody>
</table>

Drug-Drug Interactions Causing QT Prolongation

CNS

Methadone
Antipsychotics
Antidepressants

Drug-Drug Interactions Causing QT Prolongation

CNS
- Methadone
- Antipsychotics
- Antidepressants

Antimicrobial
- Macrolides
- Fluoroquinolones
- Azole Antifungals

Drug-Drug Interactions Causing QT Prolongation

CNS
- Methadone
- Antipsychotics
- Antidepressants

Antimicrobial
- Macrolides
- Fluoroquinolones
- Azole Antifungals

Gastrointestinal
- Antiemetics
- Promotility

Anesthetics/Analgesics

Volatile anesthetics: sevoflurane, halothane, isoflurane, enflurane

Methadone – QT prolonging
Fentanyl and Morphine – Not QT prolonging

Methadone

Indications: Chronic pain and opioid addiction

Usual dose range: 20 to 120mg

Kinetics: Levels increased by CYP 3A4 inhibitors, Cleared renally

Antipsychotics

Most problematic agents:
Haloperidol, Droperidol, Thioridazine

Causing QT prolongation but rarely >500 msec:
Ziprasidone, Quetiapine, Olanzapine, Risperidone

Haloperidol

Indications: Behavioral and psychotic disorders, schizophrenia, hyperactivity

Usual dose range: 0.5 to 100mg IV or PO, doses >35mg/day increase risk of QT prolongation

Kinetics: Levels increased by CYP 3A4 inhibitors

Selective Serotonin Reuptake Inhibitors

More concerning when used in combination with other QT prolonging agents

Indications: Generalized anxiety disorder, major depressive disorder, etc.

Commonly used agents: Citalopram, Escitalopram, Fluoxetine

Kinetics: Levels increased by CYP 3A4 inhibitors

Sources:
Macrolides

Azithromycin – Commonly used inpatient and outpatient antibiotic

Clarithromycin

Erythromycin – Commonly used as promotility agent

Azithromycin

**Indications:** Community-acquired pneumonia, COPD exacerbations, etc.

**Usual dose range:** 250-500mg IV/PO daily

**Kinetics:** Levels increased by CYP3A4 inhibitors

Fluoroquinolones

Levofloxacin, Moxifloxacin, Ciprofloxacin

Levofloxacin

Indications: Community-acquired pneumonia

Usual dose range: 250-750mg IV/PO Q 24-48 hours

Kinetics: Mostly excreted as unchanged drug in the urine, minimal CYP metabolism

Azole Antifungals

Fluconazole, Itraconazole, Ketoconazole, Voriconazole

More concerning when used in combination with other QT prolonging agents, especially those requiring metabolism by CYP 3A4

Fluconazole

Indications: Treatment of yeast infections, including candidiasis

Usual dose range: 200-800mg PO/IV Q 24 hours

Kinetics: Moderate inhibitor of CYP3A4, CYP2c9, Strong inhibitor of CYP2C19

Voriconazole

**Indications:** Treatment of yeast and mold infections, including aspergillus

**Usual dose range:** 4-6mg/kg IV Q 12 hours; 100-400mg PO Q 12 hours

**Kinetics:** Strong CYP3A4 inhibitor, moderate CYP2C19 inhibitor, weak CYP2C9 inhibitor

Antiemetics

High Risk for TdP: Droperidol, Chlorpromazine

Lower Risk: Ondansetron, Dolasetron

Ondansetron

Indications: Post-operative, chemo/radiation-induced nausea and vomiting

Usual dose range: 4-8mg Q 8-12 hours (doses >16mg not recommended)

Kinetics: Levels increased by CYP3A4 inhibitors

Erythromycin – macrolide antibiotic which binds motilin receptors in GI tract causing increased motility

Erythromycin

Indications: Bacterial infections, Gastroparesis (off-label)

Usual dose range: 250-500 mg IV/PO Q 6-12 hours

Kinetics: More risk of TdP with IV administration; Levels increased by CYP3A4 inhibitors

Preventative Strategies for Drug Interactions

Awareness of risk factors

Preventative Strategies for Drug Interactions

- Organ failure and impaired kinetics
- Shock and vasopressors
- Electrolyte imbalances
- CAD
- Drug-drug interactions

Preventative Strategies for Drug Interactions, continued

Monitoring

Preventative Strategies for Drug Interactions, continued

- Monitoring
  - Hepatic and renal function
  - Telemetry
  - Kinetics
  - Baseline and daily ECGs

Preventative Strategies for Drug Interactions, continued

Daily review of the patient’s medication profile

Preventative Strategies for Drug Interactions, continued

Daily review of the patient’s medication profile

Clinical Pharmacy Services

Decision Support Technology

Metabolic Interactions of QT Prolonging Agents

Level increased by CYP3A4 Inhibitors

Strong CYP3A4 Inhibitors

Metabolic Interactions of QT Prolonging Agents

Level increased by CYP3A4 Inhibitors:
- Quinidine
- Amiodarone
- Methadone
- Haloperidol
- SSRIs
- Azithromycin
- Erythromycin
- Ondansetron

Strong CYP3A4 Inhibitors

Metabolic Interactions of QT Prolonging Agents

Level increased by CYP3A4 Inhibitors:
- Quinidine
- Amiodarone
- Methadone
- Haloperidol
- SSRIs
- Azithromycin
- Erythromycin
- Ondansetron

Strong CYP3A4 Inhibitors:
- Clarithromycin
- Cobicistat
- Itraconazole
- Ketoconazole
- Posaconazole
- Telithromycin
- Voriconazole
- Protease inhibitors

Metabolic Interactions of QT Prolonging Agents, continued

Level increased by CYP2D6 Inhibitors

Strong CYP2D6 Inhibitors

Metabolic Interactions of QT Prolonging Agents, continued

Level increased by CYP2D6 Inhibitors:
- Procainamide
- Propafenone
- Flecainide

Metabolic Interactions of QT Prolonging Agents, continued

Level increased by CYP2D6 Inhibitors:
- Procainamide
- Propafenone
- Flecainide

Strong CYP2D6 Inhibitors:
- Bupropion
- Fluoxetine
- Paroxetine
- Quinidine
- Tipranavir

Poll: Test Your Understanding

You are reviewing the chart of a patient being treated for opioid addiction with methadone. Which concurrent medication raises your concern for a drug interaction that could lead to an increased risk of QT prolongation?

A. Famotidine
B. Losartan
C. Boceprevir
D. Gabapentin
You are reviewing the chart of a patient being treated for opioid addiction with methadone. Which concurrent medication raises your concern for a drug interaction that could lead to an increased risk of QT prolongation?

A. Famotidine  
B. Losartan  
C. Boceprevir  
D. Gabapentin
Poll: Test Your Understanding

In the previous patient being treated with both boceprevir and methadone, what monitoring would you recommend to prevent serious morbidity?

A. Daily chemistries including potassium and magnesium levels
B. Frequent ECG while the dose of methadone is being titrated
C. Monitoring for additional QT prolonging agents through daily chart review
D. Renal function monitoring through daily serum creatinine measurement
In the previous patient being treated with both boceprevir and methadone, what monitoring would you recommend to prevent serious morbidity?

A. Daily chemistries including potassium and magnesium levels
B. Frequent ECG while the dose of methadone is being titrated
C. Monitoring for additional QT prolonging agents through daily chart review
D. Renal function monitoring through daily serum creatinine measurement
Information Resource: https://crediblemeds.org/healthcare-providers/

### CredibleMeds QTdrugs List

<table>
<thead>
<tr>
<th>Description</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Generic Name(s)</strong></td>
<td>Quetiapine</td>
</tr>
<tr>
<td><strong>Brand Names (Partial List)</strong></td>
<td>Seroquel</td>
</tr>
<tr>
<td><strong>Current TdP risk category</strong></td>
<td>- Drugs with conditional TdP risk</td>
</tr>
<tr>
<td></td>
<td>- Drugs to be avoided by congenital Long QT</td>
</tr>
<tr>
<td><strong>Conditions for TdP if Conditional Risk Drug</strong></td>
<td>Bradycardia, Low serum K or Mg, Excessive dose, Impaired drug elimination, Use with concomitant QT/TdP drug</td>
</tr>
<tr>
<td><strong>Main Therapeutic Use(s)</strong></td>
<td>Schizophrenia</td>
</tr>
<tr>
<td><strong>Route(s) administered</strong></td>
<td>oral</td>
</tr>
<tr>
<td><strong>Market Status</strong></td>
<td>On US and non US Market</td>
</tr>
<tr>
<td><strong>Drug Label</strong></td>
<td>- QT increase mentioned</td>
</tr>
<tr>
<td></td>
<td>- Monitor QT in certain patients (Overdose)</td>
</tr>
</tbody>
</table>

You are reviewing the chart of a 49-year old female patient with no allergies, who was admitted for community-acquired pneumonia. She has been started on levofloxacin and you note that she is also taking her home medication of quetiapine. Upon researching the QT prolongation risk of quetiapine you decide to intervene to prevent morbidity in this patient. What course of action do you decide to recommend?

A. Discontinue levofloxacin and treat instead with azithromycin and ceftriaxone
B. Discontinue quetiapine during this patient’s inpatient stay
C. Monitor the ECG daily and transfer the patient to a telemetry monitoring unit
D. Discontinue the levofloxacin and treat instead with doxycycline
You are reviewing the chart of a 49 year old female patient with no allergies, who was admitted for community-acquired pneumonia. She has been started on levofloxacin and you note that she is also taking her home medication of quetiapine. Upon researching the QT prolongation risk of quetiapine you decide to intervene to prevent morbidity in this patient. What course of action do you decide to recommend?

A. Discontinue levofloxacin and treat instead with azithromycin and ceftriaxone
B. Discontinue quetiapine during this patient’s inpatient stay
C. Monitor the ECG daily and transfer the patient to a telemetry monitoring unit
D. Discontinue the levofloxacin and treat instead with doxycycline


THANK YOU for attending today’s webinar.

If you have further questions, Melinda Deubner can be reached via email at: mdeubner@beaconhealthsystem.org