Methadone and the QT Interval

Gavin Bart, MD PhD FACP DFASAM
Director, Division of Addiction Medicine
Department of Medicine
Hennepin Healthcare
Professor of Medicine
University of Minnesota Medical School
bartx005@umn.edu
Financial Conflicts

• None

• Work supported by NIDA K23DA024663
Learning Objectives

1. Learn the American Heart Association position on EKG monitoring for risk stratification for sudden cardiac death.

2. Learn methadone effect on QTc

3. Learn clinical implications of methadone and QTc prolongation
Case

• 65 year old AA male witnessed arrest
  • Collapsed while in line at methadone clinic
  • EMS V-fib then PEA
  • 34 minutes of CPR en route
  • In ED v-fib cardiovert to sinus for 10 secs
  • 31 minutes CPR in ED
• Death pronounced in ED no apparent cause
Why Did He Die?

- Hypovolemia
- Hypoxia
- Hyper/hypo K+
- Hypothermia
- Hyper/hypo glycemia
- Tablets
- Tamponade
- Tension pneumo
- Thrombosis (MI)
- Thrombosis (PE)
QTc and Torsade des Pointes

Normal
- < 450 msec men
- < 460 msec women

High risk
- > 500 msec

Rate-correction formula (Bazett's):

$$\text{QTc (msec)} = \frac{\text{QT (msec)}}{\sqrt{\text{RR (sec)}}}$$
• Case-series of 17 patients with TdP
• Mean QTc 615 msec
• Mean dose 397 mg

• 8 with ↓ K⁺ or Mg++
• 3 with structural heart disease
• 10 on contributing drugs
• 10 with bradycardia at presentation
Publication as Sentinel Event

Kao et al., 2013
Cross-Sectional

- 407 Danes on methadone
  - 32% QTc > 440 msec
  - 2% QTc > 500 msec
  - 20% past year syncope
- 200 Norwegians on methadone
  - 3.5% QTc > 500 msec
  - 1% confirmed LQTS heterozygotes

Fanoe et al., 2007; Anchersen et al. 2010
Prospective Studies

- 167 methadone patients
  - Baseline, 6 and 12 month
  - Mean baseline QTc 418.1 msec
  - Mean 6 month QTc 430.8 msec
  - 2% with QTc > 500 msec

- 421 methadone patients
  - Baseline and steady dose for ≥ 3 months
  - Mean baseline QTc 427.5 msec
  - Mean stabilized QTc 437.0 msec

Martell et al. 2005; Peles et al. 2013
Enter the guidelines

QTc interval screening for cardiac risk in methadone treatment of opioid dependence (Review)

Pani PP, Trogu E, Maremmani I, Pacini M

QT Interval Screening in Maintenance Treat Report of a SAMHSA E
To enhance patient safety

- Clinical assessment
- ECG for those at risk
- Risk stratify using QTc
- Awareness of drug interactions

Martin et al. 2011
Methadone increases QTc

So what?
Risk of Long QT-Syndrome

- **Very High Risk**
  - Secondary Prevention
  - Post-CPR or Spontaneous TdP
  - 14%

- **High Risk** (Primary Prevention)
  - Either one or more:
    - QTc > 500 msec
    - Prior syncope
  - 3%

- **Low Risk**
  - QTc ≤ 500 msec and No prior syncope
  - 0.5%

---

Goldenberg and Moss, 2008
SCD Prevalence in MMT

<table>
<thead>
<tr>
<th>Without post-mortem (35.6%)</th>
<th>With post-mortem (64.4%)</th>
<th>Total n = 90 (100%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somatic (53.3%)</td>
<td>25</td>
<td>23</td>
</tr>
<tr>
<td>Overdose (26.7%)</td>
<td>2</td>
<td>22</td>
</tr>
<tr>
<td>Traumatic (17.8%)</td>
<td>3</td>
<td>13</td>
</tr>
<tr>
<td>Unknown (2.2%)</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Total (100%)</td>
<td>32</td>
<td>58</td>
</tr>
</tbody>
</table>

Data based on 2382 patients with a total of 6450 patient-years in OMT.

- Estimated mortality rate due to QTc: 60 per 100,000
- SCD in general population: 175 per 100,000
- SCD in Minnesota: 134 per 100,000

Anchersen et al. 2009; Ray et al. 2001; MMRW 2002
1168 admissions

778 Unique Individuals

749 Individuals for Statistical Analysis

- Individuals with ECG OFF, n=406
- Individuals with ECG ON, n=346
  - Individuals w/ECG ON and OFF, n=210
    - ECG ON Predated ECG OFF, n=56
    - ECG OFF Predated ECG ON, n=154

No ECG, n=29

Bart et al., 2017
ECG Both ON and OFF (n=211)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ECG On Methadone</th>
<th>ECG Off Methadone</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at time of ECG, yrs (SD)</td>
<td>47.6 (9.7)</td>
<td>46.5 (10.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Male, %</td>
<td>57.4</td>
<td>57.4</td>
<td>—</td>
</tr>
<tr>
<td>Race, %</td>
<td></td>
<td></td>
<td>—</td>
</tr>
<tr>
<td>Caucasian</td>
<td>46.5</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>African American</td>
<td>37.4</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Asian</td>
<td>5.2</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Other</td>
<td>10.9</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>ECG setting, %</td>
<td></td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Emergency department</td>
<td>64.0</td>
<td>66.4</td>
<td>—</td>
</tr>
<tr>
<td>Inpatient</td>
<td>22.3</td>
<td>24.2</td>
<td>—</td>
</tr>
<tr>
<td>Outpatient</td>
<td>13.7</td>
<td>9.5</td>
<td>—</td>
</tr>
<tr>
<td>QTc, ms (SD)</td>
<td>440 (35)</td>
<td>429 (34)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>QTc ≥500 ms, %</td>
<td>10 (4.8)</td>
<td>4 (1.9)</td>
<td>NS</td>
</tr>
<tr>
<td>Dose, mg (range) (SD)*</td>
<td>74.5 (15–140) (26.5)</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

Average time between ECG 1.1 years (3.8)
Prospective Follow-Up

• Electronic Health Record diagnostic codes
  • January 2007-November 2011
  • ICD-9 family
    • 426 Conduction Disorders
    • 427 Cardiac Dysrhythmias
• All 749 patients queried

Bart et al., 2017
<table>
<thead>
<tr>
<th>ICD-9 Code</th>
<th>Diagnosis</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>426.12</td>
<td>MOBITZ (TYPE) II ATRIOVENTRICULAR BLOCK</td>
<td>1</td>
</tr>
<tr>
<td>426.13</td>
<td>WENCKEBACH'S PHENOMENON, HEART BLOCK</td>
<td>1</td>
</tr>
<tr>
<td>426.13</td>
<td>HEART BLOCK AV SECOND DEGREE</td>
<td>1</td>
</tr>
<tr>
<td>426.82</td>
<td>LONG Q-T SYNDROME</td>
<td>2</td>
</tr>
<tr>
<td>426.9</td>
<td>HEART BLOCK</td>
<td>1</td>
</tr>
<tr>
<td>427.1</td>
<td>IDIOPATHIC VENTRICULAR TACHYCARDIA</td>
<td>1</td>
</tr>
<tr>
<td>427.1</td>
<td>VENTRICULAR TACHYARRHYTHMIA</td>
<td>1</td>
</tr>
<tr>
<td>427.31</td>
<td>ATRIAL FIBRILLATION</td>
<td>5</td>
</tr>
<tr>
<td>427.31</td>
<td>PAROXYSMAL ATRIAL FIBRILLATION</td>
<td>1</td>
</tr>
<tr>
<td>427.41</td>
<td>VENTRICULAR FIBRILLATION</td>
<td>1</td>
</tr>
<tr>
<td>427.5</td>
<td>CARDIAC ARREST</td>
<td>3</td>
</tr>
<tr>
<td>427.61</td>
<td>PAC (PREMATURE ATRIAL CONTRACTION)</td>
<td>1</td>
</tr>
<tr>
<td>427.69</td>
<td>PVC (PREMATURE VENTRICULAR CONTRACTION)</td>
<td>3</td>
</tr>
<tr>
<td>427.81</td>
<td>SICK SINUS SYNDROME</td>
<td>1</td>
</tr>
<tr>
<td>427.89</td>
<td>BRADYCARDIA</td>
<td>12</td>
</tr>
<tr>
<td>427.89</td>
<td>SINUS TACHYCARDIA</td>
<td>1</td>
</tr>
<tr>
<td>427.89</td>
<td>SVT (SUPRAVENTRICULAR TACHYCARDIA)</td>
<td>2</td>
</tr>
<tr>
<td>427.89</td>
<td>OTHER SPECIFIED CARDIAC DYSRHYTHMIAS</td>
<td>1</td>
</tr>
<tr>
<td>427.9</td>
<td>CARDIAC DYSRHYTHMIA, UNSPECIFIED</td>
<td>9</td>
</tr>
</tbody>
</table>

- 44 diagnoses over 7064 patient years
- 18 plausibly associated with SCD (including bradycardia)
Risk of Event

- 7064 person years total
  - 44 total events = 630 per 100,000 patient years
- But only 18 events plausibly linked SCD
  - 250 per 100,000 patient years
  - Actual SCD 42 per 100,000 patient years
  - State age-adjusted SCD 134 per 100,000

*Bart et al., 2017*
Event Relationship to Methadone

- Hazard ratio 3.32 for event if QTc >
  - 450 msec for men
  - 470 msec for women

- Being on methadone at time of event did not contribute to increased HR

Bart et al., 2017
Limitations

• Retrospective chart review

• Restricted sample size

• Single site record review

• No comprehensive death registry review
QTc ≥ 440 msec

• General Population (n=3455)
  • All cause mortality: RR 1.89 (1.04-3.37)
  • Cardiac mortality: RR 3.31 (1.04-9.91)

• Healthy only (n=2269)
  • All cause mortality: RR 1.17 (0.43-2.87)
  • No relation to fatal or non-fatal cardiac events
    • RR 1.10 (0.26-13.26)

Elming et al. 1998
QTc Meta-analysis

- 7 prospective studies
- 36,000 patients
- 8.7% had QTc > 440 msec
- Death over 2-30 years of follow up
  - Increased only in those with prior CVD
  - SCD relative risk 1.0-2.1

Montanez et al. 2004
“The present data do not support the use of QT interval…for risk stratification for SCD in patients without the long-QT syndrome.”*

* for ischemic, dilated, hypertrophic cardiomyopathies
Thank You

• Zachary Wyman
• JoAn Laes
• Brad Bart
• Rehan Karim
• Scott Lenz
• NIDA