Conflict of Interest

- None
TdP: Learning objectives

◦ To review the pathophysiology of QT prolongation and TdP

◦ To become aware of the risk factors (including medication-related) for QT prolongation and TdP

◦ To understand and apply a systematic approach for dealing with drug interactions that may cause prolonged QT and TdP
Clinical Scenario

- You receive an order for a patient:
  - Levofloxacin 500 mg PO daily
  - Fluconazole 400 mg PO daily
- Your drug interaction program flags this as a major interaction due to QT prolonging effect of both drugs increasing risk for TdP.
- What do you do?
TdP: History

- Quinidine associated syncope since 1920’s
- Congenital syndromes with prolonged QT and syncope or sudden death described in 1950’s, and early 1960’s.
- 1966 Francois Dessertenne described a specific EKG form of polymorphic VT he termed “torsades de pointes”
- Over past decade single most common cause of drug withdrawal/restriction from market
- 9 structurally unrelated non-cardiac drugs: terfenadine, astemizole, grepafloxicin, terodiline, droperidol, terodiline, droperidol, lidoflazaine, sertindole, levomethadyl, cisapride
Recent FDA Warnings

- Azithromycin March 2013
- Ondansatron: 32 mg IV Dec 2012
- Domperidone >30mg/day March 2012
- Citalopram >40 mg March 2012
- Gilenya (fingolimod): Case of fatal arrhythmias Nov 2011
- Haloperidol IV >40mg/day 2007
TdP: Definition

- Polymorphic VT with a preexistent prolonged QT interval
Ventricular Action Potential

- Na$^+$
- Ca$^{++}$
- $I_{Kr}$
- $I_{Ks}$
$I_{Kr}$ Channel: hERG controlled
Delayed repolarization = prolonged QT interval
Mechanism of Torsades de Pointes

- Early afterdepolarizations
  (extra beat)
- Transmural reentry
  (Unusual pathway)
Mechanisms Of Drug - Induced QT Prolongation and Tdp

- Block of repolarizing $K^+$ currents
- Stimulation of $I_{Ca-L}$
- Stimulation of $I_{Na}$
Early afterdepolarizations
Torsades de Pointes
ECG - QT Interval
Rate-Corrected QT Interval (QTc)

- QT Interval corrected for heart rate = QTc (Bazett)

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

- General Population Average QTc = 380-400 msec
- Bazett correction has major limitations
  - Overcorrects for HR > 85 BPM
### Normal QTc Interval - Criteria

<table>
<thead>
<tr>
<th>QTc (msec)</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt;430</td>
<td>&lt;450</td>
</tr>
<tr>
<td>Borderline</td>
<td>431-450</td>
<td>451-470</td>
</tr>
<tr>
<td>Prolonged (Top 1%)</td>
<td>&gt;450</td>
<td>&gt;470</td>
</tr>
</tbody>
</table>
QTc Interval and TdP risk

- For every 10 msec increase in QTc above normal = 5-7% exponential increase in risk of TdP
- QTc > 500 msec = 2-3X increased risk for TdP

Prevention of Torsade de Pointes in Hospital Settings; *J. Am. Coll. Cardiol.* 2010;55;934-947
Assessing the risk of TdP with QT prolonging drug

- **Class 1a anti-arrhythmic agents**
  - Quinidine/ Disopyrimyde/procainamide : 2-8%

- **Class III anti-arrhythmic agents**
  - Sotalol: 2-4%
  - Ibutilide: 4-8%
  - Dofetilide 1-10%
  - Amiodarone <1%

- **Non-cardiac drugs**: 1-10/100,000
Assessing the risk of TdP with QT prolonging drug

- www.qtdrugs.org
- Risk, Possible risk, Conditional risk
Amiodarone
Arsenic trioxide
Astemizole
Azithromycin
Bepridil
Chloroquine
Chlorpromazine
Cisapride
Citalopram
Clarithromycin
Disopyramide
Dofetilide
Domperidone
Droperidol
Erythromycin
Escitalopram
Flecainide
Halofantrine
Haloperidol
Ibutilide
Levomethadyl
Mesoridazine
Methadone
Moxifloxacin
Pentamidine
Pimozide
Probucol
Procainamide
Quinidine
Sevoflurane
Sotalol
Sparfloxacin
Terfenadine
Thioridazine
Vandetanib
The Cordarone Paradox

- QT prolongation
- Low TdP risk
- Multichannel blockade:
  - Both $K_r$ & $K_s$: minimize QT dispersion
  - Na, Ca, Beta: minimize EAD
Risk factors: Non-modifiable

- History of TdP
- Congenital Long QT syndrome
- Cardiac disease
  - Heart failure
  - Hypertrophy
  - Ischemia
  - Myocarditis
Risk factors: Non-modifiable

- Epinephrine surge
  - Cocaine
  - Pheochromocytoma
  - Stroke/subarachnoid hemorrhage
  - Drug withdrawal
- Starvation
- Female (minor)
- Age?
Risk factors: Modifiable (potential ADR’s)

- Hypokalemia
- Hypomagnesemia
- Hypocalcemia (minor)
- Hypothyroid
- Bradyarrhythmias
  - Sinus bradycardia
  - Complete AV block
  - Recently terminated A fib
Risk factors: Modifiable (potential ADR’s)

◆ High QT drug concentrations (with exception of class 1a anti-arrhythmic agents):
  ◆ High dose
  ◆ Renal/hepatic dysfunction
  ◆ Pharmacokinetic drug interactions
  ◆ Fast IV infusions
  ◆ Small body habitus
Drug induced Torsades de Pointes and risk factors

- Review of all published cases of TdP associated with non-cardiac drugs
- 70 cases psychiatric medications (mainly antipsychotics)
- 69 cases antibiotics (macrolides, quinolones, azoles, antimalaerials)
- 38 cases H2 blockers (terfenadine and astemizole)
- 72 Misc (cisapride, probucol, terodiline, domperidone)

71% female
41% heart disease
40% K<4 mmol/L
39% 2 or more QT prolonging drug
- Antihistamine + antibiotic
- 2 antipsychotic drugs
- Cisapride + erythromycin
- Antibiotic + antiarrhythmic drug
35% PK interaction causing high levels of QT drug
  - Cisapride/2nd gen H2 blockers plus 3A4 inhibitors (especially erythromycin)

19% Excessive doses

18% Long QT (familial history, TdP history, long baseline QT)
  - Especially for antihistamines
- 95% had at least 1 risk factor
- 71% had 2 or more risk factors
- 35% had 3 or more risk factors
- 80% of females had additional risk factors
Patient TdP risk

- High Risk = History of TdP or LQTS
- Medium Risk = Multiple/severe risk factors
- Low Risk = Minimal/mild risk factors
Approach to patient prescribed QT prolonging drugs:

- Disclaimer: This approach is only a rough guide and should not take the place of clinical judgment!
Approach to patient prescribed QT prolonging drugs:

- Determine risk level (known, possible, conditional) for QT drugs from [www.qtdrugs.org](http://www.qtdrugs.org)

- Determine risk level for patient from Table 2
  - High risk=History of Torsades de Pointes/Congenital Long QT Syndrome
  - Medium risk Multiple/severe risk factors
  - Low risk=Minimal/mild risk factors
## Risk factors

<table>
<thead>
<tr>
<th>Non-modifiable risk factor</th>
<th>Potentially modifiable risk factor (watch for drug related causes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>- History of TdP</td>
<td>- Hypokalemia</td>
</tr>
<tr>
<td>- Congenital Long QT syndrome</td>
<td>- Hypomagnesemia</td>
</tr>
<tr>
<td>- Female</td>
<td>- Hypocalcemia</td>
</tr>
<tr>
<td>- Cardiac disease</td>
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## Approach to patient prescribed QT (prolonging) drugs:

<table>
<thead>
<tr>
<th>QT Drug Combination risk</th>
<th>High risk patient</th>
<th>Med risk patient</th>
<th>Low risk patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Known risk + known risk</td>
<td>Avoid</td>
<td>Avoid</td>
<td>Avoid</td>
</tr>
<tr>
<td>Known risk + possible/conditional risk</td>
<td>Avoid</td>
<td>EKG monitoring</td>
<td>+/- EKG monitoring</td>
</tr>
<tr>
<td>Possible/conditional risk + possible/conditional risk</td>
<td>Avoid</td>
<td>+/- EKG monitoring</td>
<td>No special monitoring</td>
</tr>
</tbody>
</table>
Approach to patient prescribed QT (prolonging) drugs:

- Determine general approach to patient from Table 1
  - Avoid: High risk, generally avoid QT drug combination
- EKG monitoring:
  - Baseline QTc >440 msec: avoid high risk drugs
  - Baseline QTc >460 msec: avoid med risk drugs
  - Baseline/On therapy* QTc >500 msec: avoid/stop all QT drugs
  - Change from baseline to on therapy* QTc > 60 msec: stop all TdP risk drugs
  - *On therapy for >= 5 x half-lives of drug
- No special monitoring: Low risk; QT drugs generally okay
Drug Interaction Resources

- Lexi-Drugs
- MicroMedex
- Facts and Comparisons
- Stockley’s
- www.torsades.org
  - Drug lists
  - Pubmed search

Yap YG, Camm AJ: Drug induced QT prolongation and TdP. *Heart* 2003;89:1363-72


www.fda.gov/ohrms/DOCKETS/ac/01/slides/3746s_01_ruskin.ppt