QT prolongation: risks and assessment

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Background

• Numerous drugs have been shown to cause QT prolongation in a dose-dependent manner
  – Post-marketing surveillance and withdrawal or warning
• QT prolongation is clearly associated with an increased risk of TdP
• No reliable criterion to identify the length of QT prolongation that is associated with a clinically significant risk of TdP
• One of the main difficulties in interpreting QT interval is its partial dependence with heart rate
• Specificities of the poisoned patient: no background ECG, how to develop risk assessment (adequate measurement of QT, heart rate correction for QT, threshold for abnormal QT)
Case observation

- 37-year-old woman, without preexisting cardiovascular disease
- Depression and chronic ethanol abuse
- Chronic treatment: fluoxetine (40 mg/day), furosemide, diazepam
- Admission after voluntary ingestion of 20 x 100 mg of trazodone
- Asymptomatic, no subjective complaints, no alteration of consciousness
- Patient was referred by the GP directly to the psychiatric unit
Case observation

– Admission ECG:
  • Normal sinus rhythm (64 bpm) with a prolonged QT interval (QT/QTc: 520/554 msec)

– Echocardiography: normal
Case observation

• Evolution
  – Severe hypotension (70/40 mmHg) on admission
  – First episode of *torsades de pointes* with marked hypokalaemia (2.7 mmol/L), normal magnesemia

– Treated by external electric countershock (EEC)
Case observation

• Evolution
  – Second episode of *torsades de pointes* with normal kalaemia treated by ECC and magnesium supplementation
  – Persistent hypotension
  – Time to ECG normalization = 6 days
Toxicokinetic data

t½β 17.8 h for trazodone (6.5 h with therapeutic doses) and 22.2 h for m-chlorophenylpiperazine (m-CPP)
Analysis of this case

• Risk factors related to the drug
  – Asymptomatic prolongation of the QT interval has been shown in healthy volunteers receiving trazodone, and occasionally after drug overdose. In contrast, there is no evidence that fluoxetine could modify the QT interval.

• Risk factors related to the patient
  – Female gender
  – Electrolyte disorders (HypoK ← furosemide)
  – Role of chronic ethanol abuse?
  – Role of psychological distress?
  – Concurrent medication: role of fluoxetine?
    • Influence on trazodone kinetics (and the metabolite)?
    • Influence on dynamics: biological effects have a longer duration than predicted by kinetics
Drugs and QT prolongation

<table>
<thead>
<tr>
<th>Cardiac drugs</th>
<th>• Amiodarone</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Sotalol</td>
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<tr>
<td></td>
<td>• Disopyramide</td>
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<td></td>
<td>• Dofetilide</td>
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<td></td>
<td>• Procainamide</td>
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<td></td>
<td>• Quinidine</td>
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<tr>
<td>Antidepressants</td>
<td>• Selective serotonin re-uptake inhibitors: citalopram, escitalopram, fluoxetine</td>
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<tr>
<td></td>
<td>• Moclobemide</td>
</tr>
<tr>
<td></td>
<td>• Tricyclic antidepressants*</td>
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<tr>
<td></td>
<td>• Lithium</td>
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<tr>
<td>Antipsychotics</td>
<td>• Amisulpride</td>
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<tr>
<td></td>
<td>• Chlorpromazine</td>
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<td></td>
<td>• Haloperidol</td>
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<td></td>
<td>• Ziprasidone</td>
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<tr>
<td></td>
<td>• Thioridazine</td>
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<tr>
<td>Antihistamines</td>
<td>• Loratadine</td>
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<tr>
<td></td>
<td>• Astemizole</td>
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<tr>
<td></td>
<td>• Diphenhydramine</td>
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<tr>
<td>Antimicrobials</td>
<td>• Ciprofloxacin, moxifloxacin,sparfloxacin</td>
</tr>
<tr>
<td></td>
<td>• Clarithromycin, erythromycin</td>
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<tr>
<td></td>
<td>• Fluconazole, voriconazole</td>
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<td></td>
<td>• Pentamidine</td>
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<tr>
<td>Other drugs</td>
<td>• Chloroquine</td>
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<tr>
<td></td>
<td>• Cisapride</td>
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<tr>
<td></td>
<td>• Dolesatran</td>
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<td></td>
<td>• Methadone</td>
</tr>
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<td>• Arsenic</td>
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</tbody>
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For more details, look directly at http://www.qtdrugs.org/medical-pros/drug-lists/drug-lists.cfm
Drugs commonly associated with TdP

<table>
<thead>
<tr>
<th>Drug</th>
<th>TdP (n)</th>
<th>Fatal (n)</th>
<th>Total (n)</th>
<th>TdP/total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sotalol</td>
<td>130</td>
<td>1</td>
<td>2758</td>
<td>4.71</td>
</tr>
<tr>
<td>Cisapride</td>
<td>97</td>
<td>6</td>
<td>6489</td>
<td>1.49</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>47</td>
<td>1</td>
<td>13725</td>
<td>0.34</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>44</td>
<td>2</td>
<td>24776</td>
<td>0.18</td>
</tr>
<tr>
<td>Ibutilide</td>
<td>43</td>
<td>1</td>
<td>173</td>
<td>24.86</td>
</tr>
<tr>
<td>Terfenadine</td>
<td>41</td>
<td>1</td>
<td>10047</td>
<td>0.41</td>
</tr>
<tr>
<td>Quinidine</td>
<td>33</td>
<td>2</td>
<td>7353</td>
<td>0.45</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>33</td>
<td>0</td>
<td>17448</td>
<td>0.19</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>21</td>
<td>6</td>
<td>15431</td>
<td>0.14</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>20</td>
<td>1</td>
<td>70929</td>
<td>0.03</td>
</tr>
<tr>
<td>Digoxin</td>
<td>19</td>
<td>0</td>
<td>18925</td>
<td>0.10</td>
</tr>
<tr>
<td>Procainamide</td>
<td>19</td>
<td>0</td>
<td>5867</td>
<td>0.32</td>
</tr>
<tr>
<td>Terodilene</td>
<td>19</td>
<td>0</td>
<td>2248</td>
<td>0.85</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>17</td>
<td>0</td>
<td>5613</td>
<td>0.30</td>
</tr>
<tr>
<td>Disopyramide</td>
<td>16</td>
<td>1</td>
<td>3378</td>
<td>0.47</td>
</tr>
<tr>
<td>Bepridil</td>
<td>15</td>
<td>0</td>
<td>384</td>
<td>3.91</td>
</tr>
<tr>
<td>Furosemide</td>
<td>15</td>
<td>0</td>
<td>15119</td>
<td>0.10</td>
</tr>
<tr>
<td>Thioridazine</td>
<td>12</td>
<td>0</td>
<td>6565</td>
<td>0.18</td>
</tr>
<tr>
<td>Flecaïnide</td>
<td>11</td>
<td>2</td>
<td>3747</td>
<td>0.29</td>
</tr>
<tr>
<td>Loratidine</td>
<td>11</td>
<td>1</td>
<td>5452</td>
<td>0.20</td>
</tr>
</tbody>
</table>

TdP (n), total number of adverse drug reaction reports which named TdP associated with this drug; Fatal (n): number of adverse drug reaction reports which named TdP with fatal outcome; Total (n): total number of adverse drug reaction reports for the drug.
Predictors of adverse cardiovascular events in suspected poisoning

- Does the occurrence of ECG abnormalities, including QTc prolongation and QT dispersion correlate with elevated risk of serious cardiac events in suspected poisoning?
  - Case control study: 34 cases compared to 101 control subjects
  - Of the 34 cases with adverse cardiovascular events
    - 19 pts with shock, 16 pts with myocardial injury, 9 pts with dysrhythmias, 15 pts with cardiac arrest
    - Toxic exposure: benzodiazepines, opioids, acetaminophen, antidepressants, antipsychotics, ethanol… with single exposure in 61%

(Manini et al., J Med Toxicol, 2010)
Predictors of adverse cardiovascular events in suspected poisoning

Table 5 Test characteristics of the optimal QTc and QTD cutpoints and the derived risk stratification for prediction of adverse cardiovascular events

<table>
<thead>
<tr>
<th>Variable</th>
<th>% Sensitivity (95% CI)</th>
<th>% Specificity (95% CI)</th>
<th>% NPV (95% CI)</th>
<th>% PPV (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>QT analysis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>QTc cutpoint (504 ms)</td>
<td>41.2 (25–59)</td>
<td>88.1 (80–94)</td>
<td>81.7 (73–88)</td>
<td>53.8 (33–73)</td>
</tr>
<tr>
<td>QTD cutpoint (70 ms)</td>
<td>58.8 (41–75)</td>
<td>69.3 (59–78)</td>
<td>84.3 (75–91)</td>
<td>40.0 (26–55)</td>
</tr>
<tr>
<td>Risk stratificationa</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Very lowb</td>
<td>94.1 (80–99)</td>
<td>49.5 (39–60)</td>
<td>96.2 (87–100)</td>
<td>38.6 (28–50)</td>
</tr>
<tr>
<td>High</td>
<td>26.5 (13–44)</td>
<td>95.0 (89–98)</td>
<td>79.3 (71–86)</td>
<td>64.3 (35–87)</td>
</tr>
</tbody>
</table>
Mechanisms of drug-induced QT prolongation

- Blockade of the delayed rectifier potassium channel ($I_{KR}$), which is coded by hERG
- Prolongation of the action potential, lengthening of QT
- Delayed repolarization $\Rightarrow$ early after depolarizations
  - Focal activity
  - Re-entrant pathways $\Rightarrow$ TdP
Non-drug risk factors and the QT interval

• Classical presentation of QT prolongation and TdP with congenital long QT syndromes
  – Romano-Ward, Jervelle, Lange-Neilsen syndrome
  – Variety of mutations in ion channel sub-units (potassium and sodium channels) and mutations in regulatory protein coding genes

• But even in « healthy » subjects, QT interval is a heritable trait and genetic variants are probably the most important factor determining the risk to develop QT prolongation after exposure to some drugs
  – These patients are likely to have normal ECG morphology and normal or near normal QT off the drug

(Isbister et al., Br J Clin Pharmacol, 2013)
Non-drug risk factors and the QT interval

- Other physiological or pathological factors
  - Female gender > 20 ms (normal range QTc?: 440 ms for men, 460 ms for women)
  - Increase of QT interval with aging
  - Diurnal variation of QT interval
  - In clinical practice, the most common pathological conditions associated with QT prolongation are electrolyte disturbances
    - HYPOKALIEMIA, HYPOCALCEMIA, HYPOMAGNESESEMIA
  - Other conditions: myocardial ischemia, cardiomyopathies, hypothyroidism, obesity, hypertension....

The key issue: which are the factors increasing independently the risks for TdP in patients with prolonged QT?

(Isbister et al., Br J Clin Pharmacol, 2013)
Medications known to inhibit CYP3A4

- **Antifungals**
  - Itraconazole
  - Ketoconazole

- **Antidepressants**
  - Nefazodone
  - Fluvoxamine

- **Grapefruit juice**

- **Antibiotics**
  - Erythromycin
  - Clarithromycin

- **Antivirals**
  - Ritonavir
  - Indinavir
  - Nelfinavir

- **Calcium channel blockers**
  - Diltiazem

How to measure the QT interval?

- Multiple considerations
  - Manual or automated?
  - End of the T wave?
  - Which lead? Single or multiple? Median, maximum or mean?

(Isbister et al., Br J Clin Pharmacol, 2013)
How to measure the QT interval?

• The point where the T wave returns to the isoelectric line
• Single lead: II, longest QT about 60% of the time
• Multiple leads and median measurement
• Multiple beats, multiple leads and median
• Manual or automatic measurement?
  – Manual: accurate assessment of the end of QT
• Automatic measurement on the 12-lead ECG?
  – Not fully reliable

Simplified method
  – Manual measurement of the QT interval in 6 leads, in one complex
  – Visual determination of the end of T wave
  – Use of median QT interval

(Isbister et al., Br J Clin Pharmacol, 2013)
Correction of QT for HR

<table>
<thead>
<tr>
<th>Name</th>
<th>Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bazett’s Correction</td>
<td>$QT_c = \frac{QT}{RR^{0.5}}$</td>
</tr>
<tr>
<td>Fridericia’s Correction</td>
<td>$QT_c = \frac{QT}{RR^{0.33}}$</td>
</tr>
<tr>
<td>Framingham Correction</td>
<td>$QT_c = QT + 0.156 \times (1 - RR)$</td>
</tr>
</tbody>
</table>

QT in ms and RR in s.
Correction of QT for HR and risk assessment

• The dependency of QT interval on heart rate is not completely resolved by the correction formulae, including Bazett’s
  – Over-correction for fast HR
  – Ex: quetiapine overdose causes QTc prolongation, but no reports of TdP

• The QT/HR relationship is stable within an individual but varies significantly between individuals

• Cut-off ? 440 ms in men, 460 ms in women ?

• An absolute QT or QTc > 500 ms is often considered as a significant risk for TdP

(Isbister et al., Br J Clin Pharmacol, 2013)
What is the interest of QT nomogram?

- «Cloud» diagram: plot of QT vs RR interval for a population
  - QT-RR plots in individuals (variability of the QT-RR relationship over a 24 h period)
  - Population «cloud» obtained by the superimposition of the individual clouds
  - QT-RR pairs outside the population «cloud» => increased risk of arrhythmia

(Fossa et al., J Pharmacol Exp Ther, 2005)
Application of the QT nomogram to a poisoned population

- Systematic review of cases of drug-induced TdP
- Controls: pts with non-cardiotoxic drugs in overdose who did not develop TdP
- Comparison between QT nomogram and curves corresponding to QTc 440 ms and QTc 500 ms
  - 139 « cases » included with a large variety of toxins, compared to 318 controls

(Chan et al., Q J Med, 2007)
The TdP cases occurred primarily at lower HR values with longer QT interval (most of the cases with HR 30-90/min).

The QT-HR pairs for the TdP cases fell predominantly above the QT nomogram at risk line, with some limitation for the extrapolated part of the nomogram.

(Chan et al., Q J Med, 2007)
Sensitivity and specificity

The QT nomogram has a high sensitivity and specificity for cases of drug-induced TdP.

- Bazett’s formula: propensity to overcorrect QT at fast heart rates (>70/min) and to undercorrect QT at slow heart rates (<50/min).
- Special interest for bradycardic pts (<60/min).
- Relative protective effect of tachycardia in the development of TdP.

### Table 3: Sensitivity and specificity (95%CI) of the QT nomogram, compared to Bazett’s QTc = 440 ms and QTc = 500 ms

<table>
<thead>
<tr>
<th></th>
<th>QT nomogram (with extrapolation)</th>
<th>QT nomogram (no extrapolation)*</th>
<th>Bazett’s QTc = 440</th>
<th>Bazett’s QTc = 500</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>96.9% (93.9–99.9)</td>
<td>98.3% (96.1–100)</td>
<td>98.5% (96.4–100)</td>
<td>93.8% (89.6–98.0)</td>
</tr>
<tr>
<td>Specificity</td>
<td>98.7% (96.8–100)</td>
<td>99.3% (97.8–100)</td>
<td>66.7% (58.6–74.7)</td>
<td>97.2% (94.3–100)</td>
</tr>
</tbody>
</table>

*In this analysis, all cases with HR >104 bpm were excluded from analysis, so that only the original QT nomogram was used.*
Evaluation of QT nomogram after antidepressant overdose

• Methods
  – Retrospective case control study of patients presenting to the hospital after overdose of citalopram, mirtazapine and venlafaxine
  – Primary outcome variable: QT higher than nomogram, compared with QTc ≥ 440 ms and ≥ 500 ms, comparison between drugs

(Waring et al., Br J Clin Pharmacol, 2010)
Results

- 858 ECG from 541 pts
- Median stated dose ingested similar in the 3 groups
- None of the pts developed TdP or significant arrhythmia
- The proportion of pts with QT ≥ nomogram was 2.4% (23.1% for QTc ≥ 440 ms and 1.1% for QTc ≥ 500 ms)
- Greater likelihood of QT ≥ nomogram with citalopram

(Waring et al., Br J Clin Pharmacol, 2010)
Evaluation of QT nomogram after antidepressant overdose

• Results
  – A higher proportion of pts in the citalopram group had QTc ≥ 440 ms

(Waring et al., Br J Clin Pharmacol, 2010)
Evaluation of QT nomogram after antidepressant overdose

• Potential advantages of the nomogram
  – Low false positive rate (2% vs 23% with cut-off 440 ms)
  – Better identification of the pts at the highest risk of significant arrhythmia
  – Nomogram more sensitive for the pts with HR 30-60/min (undercorrection of QT interval for lower HR with Bazett’s formula)
  – Among a population of patients poisoned by antidepressants, identification of substances with higher risk (citalopram, amisulpride)
Evaluation of the QT nomogram

(Isbister et al., Br J Clin Pharmacol, 2013)
Citalopram, QT prolongation and TdP

• After therapeutic doses
  – Reports of prolonged QT
  – Swedish pharmacovigilance: citalopram in 10% cases of TdP
  – Comparison 20 mg versus 60 mg

(Cooke et al., Eur J Clin Pharmacol 2013)
Citalopram, QT prolongation and TdP

- Toxicity in the setting of citalopram overdose
  - QTc significantly higher in cases evolving citalopram than either fluoxetine, fluvoxamine, paroxetine or sertraline; 68% of citalopram overdose pts had QTc > 440 ms
  - Clear relationship between QTc prolongation and citalopram concentrations within a toxic range
  - Administration of activated charcoal may decrease the risk of QT prolongation after citalopram overdose
Prior to commencement, obtain a baseline ECG. Ideally collect ECGs at different time periods or a 24 h 12-lead Holter assessment.

Manually measure the QT interval as outlined in Table 2.

Plot the QT-heart rate pair on the QT nomogram.

If the QT-heart rate pair is below the nomogram line, then commence the medication.

Obtain repeat ECGs after commencement and re-plot the QT-heart rate pair on the nomogram.

If the QT-heart rate pair remains below the nomogram line, continue the medication.

If the QT-heart rate pair is above the nomogram line, consider other medications that are not known to prolong the QT interval.

Consider discontinuing the medication if the QT-heart rate pair is above the nomogram line.
Conclusions

• Many antipsychotic and antidepressant drugs are known to prolong the QTc interval in a dose-dependent manner
  – But TdP remains a rare tachyarrhythmia and the risk of TdP cannot be precisely estimated
• Importance of individual factors, electrolyte disturbances, drug interactions…
• Limitations of correction formulae for QTc: usefulness of QT nomogram
• QT nomogram does not quantify the risk or probability of TdP occurring
• Risk/benefit ratio when prescribing drugs that cause QT prolongation (methadone)