Racial-Ethnic Association with QT Prolongation Following Acute Drug Overdose

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QT Interval

- Electrical depolarization and repolarization of the left and right ventricles
- Sodium, calcium and potassium current
- Varies with heart rate:
  - Faster heart rate → shorter the QT interval
  - Must be corrected (QTc)

Determinants of QT Interval

- Factors associated with baseline QT interval:
  - Race (whites 5-10 ms > blacks)
  - Genetic (chromosome 7 and 11)
  - Gender (females 10 ms > males)
  - Age (increase trend)

- Role of above factors in drug-induced QT changes:
  - Extrapolation unclear:
    - Therapeutic vs OD?
    - Baseline vs Drug-induced?

Myocardial Sensitization

- Altered substrate
- Triggered event

QT Risk Categories: Acute Drug Overdose

- Normal QTc
- Long QTc (but < 500 ms)
- Severe QTc ≥ 500 ms

- Risk of CV events:
  - Shock
  - MI
  - VT/VF
  - Cardiac Arrest

- Risk of death:
  - Low Risk: 3.8%
  - High Risk: 26%
  - Highest Risk: > 50%
Study Objectives

- **Aim:**
  - To evaluate the association between:
    - Race/Ethnicity
    - Drug-induced QT prolongation

- **Target Population:**
  - ED patients with acute drug overdose

Study Methods

- **Design:** Cross sectional observational study over a 2 year period
- **Setting:** Urban teaching hospitals
- **Subjects:** Adult ED patients with acute drug overdose, racially diverse
- **Data:** Demographics, race/ethnicity, drug class, QTc

Definitions

- Race/ethnicity by chart (facesheet and ECG)
  - (a) Race (4 codes): White, Black, Asian, or other
  - (b) Ethnicity (2 codes): Hispanic or not

- Outcome = Prolonged QTc
  - Initial ECG computer generated QTc (Bazzett)
  - 460 ms (men) or 470 ms (women)

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

Statistical Analysis

- Factors associated with QT prolongation were assessed with chi-squared, t-test, and logistic regression analysis

- **Sample Size:**
  - 20% risk factor prevalence
  - 10% QT prolongation
  - Need 466 patients (80% power, 2-fold RD)

Results: Enrollment

- QT prolongation occurred in 11.7%
  - 95% CI = 9.0-14.4

Racial-ethnic Composition

- **Race**
  - 38% White
  - 21% Black
  - 10% Asian
  - 31% other
- **Hispanic Ethnicity**
  - 19% Hispanic
  - 64% Other-Hispanic
  - 34% Uncoded-Hispanic
  - 2% White-Hispanic
Results

<table>
<thead>
<tr>
<th>Race/Ethnicity:</th>
<th>Prolonged QTc</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Univariate</td>
</tr>
<tr>
<td></td>
<td>OR</td>
</tr>
<tr>
<td>Hispanic</td>
<td>0.53</td>
</tr>
<tr>
<td>Black</td>
<td>2.2</td>
</tr>
</tbody>
</table>

* Model included significant co-variates: age, heart rate, and serum potassium.
- Asians, White both non-significant.
- Abbreviations: bpm = beats per min; CI = confidence interval; OR = odds ratio

DRUGS CORRELATED WITH QT PROLONGATION

<table>
<thead>
<tr>
<th>Drugs / Drug Class:</th>
<th># Single (%) QTP</th>
<th># Multi-drug (%) QTP</th>
<th># Total (%) QTP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opioids</td>
<td>15 (40)†</td>
<td>69 (19)†</td>
<td>84 (23)†</td>
</tr>
<tr>
<td>Methadone**</td>
<td>4 (0)</td>
<td>31 (26)†</td>
<td>35 (23)†</td>
</tr>
<tr>
<td># Methadone</td>
<td>11 (55)†</td>
<td>38 (13)</td>
<td>49 (22)†</td>
</tr>
<tr>
<td>Sympathomimetics</td>
<td>10 (60)†</td>
<td>48 (15)</td>
<td>58 (22)†</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>8 (38)†</td>
<td>39 (5)</td>
<td>47 (11)</td>
</tr>
<tr>
<td>Citalopram**</td>
<td>0</td>
<td>10 (0)</td>
<td>10 (0)</td>
</tr>
</tbody>
</table>

| TTOTALS            | 279 (13)         | 263 (10)             | 542 (12)        |

| Abbreviations: QTP = QT prolongation (460 ms male, 470 ms female).

Drug Class QT Risk Within Race/Ethnicity

<table>
<thead>
<tr>
<th>Characteristic:</th>
<th>No. (% QTP)</th>
<th>OR</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HISPANIC</td>
<td>196 (8.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multidrug Overdose</td>
<td>17 (100)</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Opioids</td>
<td>37 (30)</td>
<td>10.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Methadone</td>
<td>14 (40)</td>
<td>5.2</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td># Methadone</td>
<td>23 (30)</td>
<td>7.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BLACK</td>
<td>78 (19.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multidrug Overdose</td>
<td>15 (100)</td>
<td></td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

| Abbreviations: CI = confidence interval; OR = odds ratio; QTP = QT Prolongation.

Discussion

- Race/ethnicity highly correlated with QT risk
  - Blacks > 2.5-fold increased QT prolongation (QTP)
  - Hispanics had >50% reduction in QTP risk
  - Vulnerability to QTP in multidrug overdose

- Genetic vulnerability or vice versa?
  - Major concern in Black population:
    - Shorter QT baseline
    - Higher QTP following overdose

- Further evidence of QTP in opioid OD
  - Not just methadone!
  - Non-methadone opioids highly significant correlation with QTP in single-drug OD
  - Novel finding: Hispanics highly vulnerable

- Lack of CERT QT drugs surprising?
  - Therapeutic dose ↦ extrapolate to OD?
  - Not well represented
  - Limited utility for poisoning?

Limitations

- Baseline ECG
  - Drug-induced vs. Congenital Long QT syndrome
- Not self-reported
  - 5-10% inaccuracy in literature
- Exposure confirmation incomplete
- Sedative use for agitation
- Urban diverse setting
  - May not generalize to all settings
Conclusions

- In this large urban study of acute drug overdose, race/ethnicity predicted QT prolongation:
  - Blacks had over 2.5-fold increased risk
    - Highly vulnerable to multidrug OD
  - Hispanics had over 50% risk reduction
    - Highly vulnerable to opioids, multidrug OD

Conclusions (continued)

- We identified high/low risk drug classes
  - Opioids including non-methadone subgroup
  - Sympathomimetics
  - Unable to implicate CERT QT drugs

Ongoing Study

- To explore racial QT risk in drug overdose:
  - Drug class associations
  - Adverse cardiovascular outcomes
  - Genetic polymorphisms

Thank You

- Barry Stimmel MD
  Cardiology Division
  Mount Sinai School of Medicine
  New York, NY USA

- David Vlahov PhD
  Dean, UCSF School of Nursing
  San Francisco, CA USA

Sensitivity Analysis

- Assuming up to 10% race misclassification
  - 12% QT prolongation in dataset

- Hispanics
  - OR 0.62 (CI 0.33–1.0) p=0.05

- Blacks
  - OR 1.9 (CI 1.02–3.5) p<0.05
### Severe QT Prolongation (>500)

- 8/15 (53%) multi-drug overdose
- 6/15 (40%) ≥1 CERT drug

**Numbers of occurrences:**
- 1/15: 15 drugs (two CERT 3, one CERT 2)
- 2/15: Alprazolam, APAP, cocaine, diazepam
- 3/15: Methadone (CERT 1)

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**DRUGS NOT CORRELATED WITH QT PROLONGATION**

<table>
<thead>
<tr>
<th>Drugs / Drug Class</th>
<th># Single OD (% QTP)</th>
<th># Multi OD (% QTP)</th>
<th># Total (%QTP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzodiazepines</td>
<td>10 (20)</td>
<td>75 (13)</td>
<td>85 (14)</td>
</tr>
<tr>
<td>OTC Drugs</td>
<td>16 (19)</td>
<td>55 (5)</td>
<td>71 (8)</td>
</tr>
<tr>
<td>Diphenhydramine**</td>
<td>12 (8)</td>
<td>16 (6)</td>
<td>28 (7)</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>11 (18)</td>
<td>39 (5)</td>
<td>50 (8)</td>
</tr>
<tr>
<td>Quetiapine**</td>
<td>5 (0)</td>
<td>22 (9)</td>
<td>27 (7)</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>7 (14)</td>
<td>19 (0)</td>
<td>26 (4)</td>
</tr>
<tr>
<td>TOTALS</td>
<td>279 (13)</td>
<td>263 (10)</td>
<td>542 (12)</td>
</tr>
</tbody>
</table>

**Abbreviations:**
- OTC = over the counter
- QTP = QT prolongation

**Class by AZ CERT**
1. Highest Risk
2. Possible Risk
3. Conditional Risk

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**Abstract**

The rapid progress currently being made in genome science has created interest in genetic selection; however, clinical decision-making has been hindered by the lack of population genetics data available to guide individualized medicine. The development of drugs and the structure of a drug-adaptive pathway is dependent upon the genetics of the host. Genetic variants affect the ability of a drug to modify particular pathways, and the drug-adaptive pathway is a key component of the drug response. The identification of such pathways is of great interest as it allows for the development of more effective personalized medicine approaches.

**Methods and Findings:**

To describe the homozygosity in a unidimensional sample we used the Mafa 312 genotyping assay. The 1000 Genomes project, a large-scale international consortium that aims to identify the genetic diversity of the human population, was used to assess the genetic diversity of the homozygous variants. The 1000 Genomes project identified 9,478 unique homozygous variants in the sample, of which 1,214 were associated with QT prolongation. The study was conducted at the University of Wisconsin, Madison, WI, USA, New York University School of Medicine, Department of Pharmacology and Toxicology, and the University of Wisconsin-Madison School of Medicine and Public Health. The study was supported by NCI 2R01CA134589 and the University of Wisconsin-Madison School of Medicine and Public Health.

**Conclusion:**

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**AZ CERT Drug = Appears on QT-drug list from the Arizona Center for Education and Research on Therapeutics available at www.qtdrugs.org.**