Reports of Torsades de Pointes (TdP) Associated with Intravenous (IV) Drug Formulations that Contain the Preservative Chlorobutanol (CB)

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INTRODUCTION

Torsades de Pointes polymorphic ventricular tachychardia

Chlorobutanol: a chemical preservative used in many IV drug and vitamin formulations

- Weak inhibitor of K⁺ ion channels

Synergistic CB-Drug Interactions

CB has been found to potentiate the HERG inhibition caused by Terfenadine and Methadone

PURPOSE

To examine the association between use of CB containing drug formulations and the occurrence of QT prolongation and TDP
METHODS

- Drugs with injectable formulations containing CB were identified using dailymed.nlm.nih.gov

- A PubMed search was performed
  - Thorough QT studies
  - Case studies
  - Clinical trials

- The FDA’s adverse event report system (FAERS) was queried (using Oracle’s Empirica Signal) for relevant case reports

- Individual reports were reviewed
  - Route of administration
  - Confounding factors
  - Duplicate cases
Dailymed lists 9 drugs currently on the US market that contain CB in their IV formulation (listed below)

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>QT N</th>
<th>QT EB05</th>
<th>TdP N</th>
<th>TdP EB05</th>
<th>QT prolongation in literature</th>
<th>TdP in literature</th>
<th>HERG IC50</th>
<th>Dose of CB received @ usual drug dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methadone</td>
<td>504</td>
<td>9.11***</td>
<td>367</td>
<td>23.1***</td>
<td>•</td>
<td>•</td>
<td>•</td>
<td>25-500</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>56</td>
<td>1.49</td>
<td>37</td>
<td>3.08***</td>
<td>•</td>
<td>•</td>
<td>•</td>
<td>1.5</td>
</tr>
<tr>
<td>Estradiol</td>
<td>54</td>
<td>.532</td>
<td>9</td>
<td>.151</td>
<td>•</td>
<td>•</td>
<td>•</td>
<td>10</td>
</tr>
<tr>
<td>Vasopressin</td>
<td>5</td>
<td>.812</td>
<td>7</td>
<td>1.92</td>
<td>•</td>
<td>•</td>
<td>•</td>
<td>2.5 mg q 3 hr.</td>
</tr>
<tr>
<td>Testosterone</td>
<td>17</td>
<td>.237</td>
<td>7</td>
<td>1.92</td>
<td>•</td>
<td>•</td>
<td>•</td>
<td>10</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>14</td>
<td>.432</td>
<td></td>
<td></td>
<td>•</td>
<td></td>
<td></td>
<td>7.5 – 22.5</td>
</tr>
<tr>
<td>Desmopressin</td>
<td>11</td>
<td>.548</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>35</td>
</tr>
<tr>
<td>Papaverine</td>
<td>8</td>
<td>1.87</td>
<td></td>
<td></td>
<td>•</td>
<td>•</td>
<td>•</td>
<td>1.5</td>
</tr>
<tr>
<td>Oxytocin</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>20</td>
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EB05: Lower bound of Bayesian risk estimate (relevant signal = >2)
***denotes relevant result
RESULTS: Papaverine

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Intracoronary Papaverine in published literature

- Documented QT prolongation
- 21 cases of TdP
- 1.2% of patients treated with Papaverine developed TdP


10 mg IC Papaverine

Papaverine block of HERG in HEK293 cells
RESULTS: Methadone

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Methadone prolongs the QT interval

Chlorobutanol (3 mM) + Methadone:

Methadone’s QT prolongation with CB synergistically blocks HERG
LIMITATIONS

FAERS

• FAERS queries using Empirica lack route specificity

Literature

• Laboratory experiment information is incomplete regarding CB as an ingredient
• CB is a preservative used in injectable formulations of 9 drugs
• CB is an inhibitor of HERG current
• CB potentiates the HERG block of Terfenadine and Methadone
• Clinical reports of QT prolongation and TdP with other CB containing drug formulations indicates that CB could be potentiating the HERG block of those drugs
• CB is not in the formulations of these drugs in Europe
• CB was used in morphine formulations, now removed
• CB poses a potential risk, and its inclusion in IV formulations is unnecessary