Drug Induced QT Prolongation

The QT interval is measured from the beginning of the QRS interval to the end of the T wave. Manual measurement is preferred. Because QT interval shortens when heart rate is increased, corrected QT (QTc) using Bazett’s formula is commonly used. The QT length represents the entire duration of ventricular systole and the repolarization to resting state. Efflux of potassium drives this repolarization. When it is hindered, such as by a pharmacologic agent, ventricular repolarization is slowed and the QT interval becomes prolonged. Slowing of repolarization can set the heart up for early after depolarizations. In some cases this can progress to polymorphic ventricular tachycardia (torsades de pointes, TdP).

Inhibition of potassium efflux is a property shared by an array of drugs. Some QT prolonging drugs may be more likely to precipitate TdP than others based upon pharmacologic differences that are incompletely understood. Higher serum concentrations and additive drug effects can increase the risk. Other risk factors for acquired QT prolongation include electrolyte abnormalities (hypokalemia, hypocalcemia, and hypomagnesemia), myocardial ischemia, bradycardia, and hypothermia. Prolonged QRS alone can cause apparent increase in the QT interval. Women and those with advanced age are at an increased risk. Genetic variations in the expression of potassium channels may also increase some individuals’ susceptibility to drug induced QT prolongation.

Experts disagree on the length at which a QTc interval is prolonged and at which it becomes clinically concerning for TdP. Complicating this assessment is evidence that QTc interval prolongation does not appear to have a linear relationship with TdP occurrence. In a recent international survey among medical toxicologists, most respondents considered a QTc interval prolonged when it is > 450 msec in men and > 460 msec in women. However, 15% did not consider QTc prolonged until it was >500 msec. The Substance Abuse and Mental Health Services Administration has considered 500 msec as the threshold for long QT among methadone patients. Some evidence has shown an association of QTc >500 msec with a 2-3 times higher incidence of TdP. The presence of bradycardia in addition to QTc prolongation increases the risk of TdP.

If QTc prolongation occurs, offending agents should be identified and removed where possible. Electrolytes should be corrected. Magnesium should be maintained between 1-2 mEq/L and potassium between 4.5-5 mEq/L. While potassium shortens QTc interval, magnesium suppresses recurrent TdP without shortening QTc. If TdP occurs, 1-2g of IV magnesium should be administered and repeated if necessary. The use of magnesium prophylactically for long QT with no TdP is debated and not well studied. For recurrent episodes of TdP, cardiac overdrive pacing or isoproterenol may be considered.

Common Drugs That Prolong QT

<table>
<thead>
<tr>
<th>Category</th>
<th>Drugs</th>
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</thead>
<tbody>
<tr>
<td>Antiarrhythmics</td>
<td>procainamide, quinidine, sotalol, amiodarone, flecainide</td>
</tr>
<tr>
<td>Anti-infectives</td>
<td>clarithromycin, erythromycin, azithromycin, ciprofloxacin, fluconazole, levofloxacin, moxifloxacin</td>
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<tr>
<td>Antiemetics</td>
<td>droperidol, IV ondansetron</td>
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<tr>
<td>Antipsychotics</td>
<td>chlorpromazine, haloperidol, ziprasidone, thioridazine</td>
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<tr>
<td>Antidepressants</td>
<td>citalopram, escitalopram</td>
</tr>
<tr>
<td>Other drugs</td>
<td>donepezil, methadone, cocaine, propofol</td>
</tr>
</tbody>
</table>

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QTc Prolonging Drugs

References


