QT prolongation and drug-drug interactions

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Disposition

• Introduction to QT prolongation
• Three relevant DDI scenarios
• Concluding reflections
The QT interval

- The QT interval of the ECG reflects the cardiac ventricular action potential duration. This is largely determined by the rapidly activating delayed rectifier current (Ikr), conveyed by the hERG voltage-dependent potassium channel.
- QT interval is also heart rate dependent (shortened with increasing heart rate); therefore, a correction factor is generally used (QTc).
- Oft-cited upper limit of normal: Men – 440 ms; women – 450 ms.
QT prolongation and torsade de pointes

- Excessive QTc interval prolongation can be proarrhythmic and prompt a potentially fatal ventricular tachyarrhythmia known as torsade de pointes (TdP), which translates as “twisting of the point” (beat to beat change in the electrical axis)

- May be self terminating, or degenerate into ventricular fibrillation (approx 7-20% of cases)

Figure 1. Onset of TdP during the recording of a standard 12-lead ECG in a young male with a history of drug addiction treated with chronic methadone therapy who presented to a hospital emergency department after ingesting an overdose of prescription and over-the-counter drugs from his parent’s drug cabinet. Classic ECG features evident in this rhythm strip include a prolonged QT interval with distorted T-U complex, initiation of the arrhythmia after a short-long-short cycle sequence by a PVC that falls near the peak of the distorted T-U complex, “warm-up” phenomenon with initial R-R cycles longer than subsequent cycles, and abrupt switching of QRS morphology from predominately positive to predominately negative complexes (asterisk).
Drug induced QT-prolongation

Drug induced QT prolongation is generally due to effects on the hERG channel, which carries the Ikr.

hERG channel blocking is presumed to be the usual mechanism, but hERG channel trafficking to the cell membrane may also be impacted, as evidenced, e.g., by time-dependent effects in vivo for some drugs.

hERG channel blocking is the mechanism of action of class III antiarrhythmics (e.g., sotalol, dofetilide).
hERG channel block as well as QT prolongation are imperfect biomarkers of TdP risk (High NPV; lower PPV)

While virtually all drugs that prolong the QT interval and cause TdP also block Ikr, this finding is not specific, since many drugs that do not appear to cause TdP also block this current (e.g., verapamil).

Some drugs considerably prolong the QTc without being strongly associated with TdP (e.g., amiodarone) presumably due to counteracting effects on other cardiac ion channels.
Patient factors are of considerable importance for the risk of drug induced TdP

- In general, with increasing QTc interval comes an increasing risk of TdP
- The absolute magnitude of TdP risk relating to a certain level of QT prolongation is ill defined for non-cardiac drugs
- Absolute QTc >500 ms, or increase from baseline >60 ms is often cited as thresholds of concern for the individual patient. The proportion of patients exceeding these values should be cited in regulatory submissions.
- The risk of TdP also considerably depends on a number of host factors, including, e.g., female gender, electrolyte abnormalities, myocardial ischaemia, congestive heart failure, bradycardia, pre-existing prolongation of the QT interval
The thorough QT study (ICH E14)

- Study in healthy volunteers to determine whether a drug has a threshold pharmacological effect on cardiac repolarisation, as detected by QT/QTc prolongation; does not per se establish that a drug is torsadogenic
- Moxifloxacin generally used as positive control to ascertain assay sensitivity
- The threshold level of regulatory concern is an increase of around 5ms, as evidenced by an upper bound for the 95% confidence interval of 10ms
- Drugs that prolong the mean QTc interval by >20ms are considered to have a substantially increased risk of being proarrhythmic
- If the QTc study is positive, additional evaluation of cardiac safety in clinical trials is generally mandated (e.g., ECG monitoring, focus on AEs of special interest)
With moxifloxacin and many other drugs, peak QTc prolongation roughly coincides with Tmax; however this is not always the case.

Pronounced hysteresis of the saquinavir effect on QTc. From Zhang et al, 2012.
QTc and DDIs: scenarios

a) A metabolic inhibitor is combined with a QTc prolongator (PK interaction)

b) A drug that is a combined QTc prolongator as well as a metabolic inhibitor is combined with a QTc prolongator (PK + PD interaction)

c) A QTc prolongator is combined with another QTc prolongator (PD interaction)
a) A metabolic inhibitor is combined with a QTc prolongator
QT prolongation and DDI; the terfenadine case

• Prompted regulatory attention to drug induced LQTS
• Widely used antihistamine with 16 million US prescriptions in 1991
• Terfenadine is a prodrug, biotransformed into the active compound fexofenadine by CYP3A; under normal conditions (recommended dose, no significant liver disease, no DDIs), little terfenadine reaches the systemic circulation
• The active moiety, fexofenadine, is not a significant QT prolongator
In overdose, or in the presence of a potent CYP3A inhibitor, terfenadine becomes torsadogenic.

From Monahan et al, 1990
On co-administration with ketoconazole, systemic terfenadine exposure increased several-fold (Honig et al 1993)

Of note, all subjects but one had undetectable terfenadine levels when given without ketoconazole; the remaining subject had a peak level of 7 ng/mL
Terfenadine exposure was correlated to change in QTc interval (Honig et al 1993)

ECGs at baseline, at terfenadine ss, and during ketoconazole coadministration

**Fig 4.**—Trough concentration vs trough change in corrected QT intervals for all measured points in the study. Regression line has an $R^2$ of .6; $P=.0001$. 
Healthy volunteer cross-over study with cisapride and clarithromycin (van Haarst et al, 1998)

- Minimal QTc increase with clarithromycin alone
- 6ms increase from baseline with cisapride 10 mg x 4
- On co-administration cisapride exposure (Cmax, AUC) increased approximately threefold, and QTc increased to 25ms above baseline; maximal effects correlated with cisapride Tmax
The Pfizer 128-054 study

- Randomised study in patients with psychotic disease, comparing the QTc prolonging effect of 6 different antipsychotics, alone and in combination with a relevant metabolic inhibitor (CYP1A2 fluvoxamine; CYP2D6 paroxetine; CYP3A ketokonazole)
- Doses titrated to "maximally tolerated dose" or protocol specified maximum
- ECGs were obtained at baseline and at steady state with each treatment period, at the presumed Tmax for each drug
Outcomes do not tell an entirely simple story

N approx 30 per group

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<thead>
<tr>
<th></th>
<th>ziprasidone</th>
<th>risperidone</th>
<th>olanzapine</th>
<th>quetiapine</th>
<th>thioridazine</th>
<th>haloperidol</th>
</tr>
</thead>
<tbody>
<tr>
<td>QTc (Bazetts formula) increase over baseline at steady state (ms)</td>
<td>20.6</td>
<td>10.0</td>
<td>6.4</td>
<td>14.5</td>
<td>35.8</td>
<td>4.7</td>
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<tr>
<td>Exposure increase with metabolic inhibitor</td>
<td>x1.39 (ketoconazole)</td>
<td>x2.47 (Paroxetine or ketoconazole)</td>
<td>x1.77 (Fluvoxamine)</td>
<td>x4.03 (ketoconazole)</td>
<td>x1.04 (paroxetine) NO INCREASE</td>
<td>x1.94 (paroxetine and ketoconazole)</td>
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<tr>
<td>QTc increase over baseline with metabolic inhibitor</td>
<td>20.4</td>
<td>3.2</td>
<td>5.3</td>
<td>19.7</td>
<td>28.0</td>
<td>8.9</td>
</tr>
</tbody>
</table>

(report available at: http://www.fda.gov/ohrms/dockets/ac/00/backgrd/3619b1a.pdf)
b) A combined QTc prolongator and metabolic inhibitor is combined with a QTc prolongator
The interaction between domperidone 10mg x 4 and ketoconazole 200mg x 2 (Boyce et al, 2011)

- Domperidone is an antiemetic dopamine antagonist with a bioavailability of approx 15%
- High dose (10mg/kg per 24 h) i.v. therapy associated with QT-prolongation and TdP
- Biotransformed by CYP3A
- Ketoconazole not only CYP3A inhibitor, but also associated with mean increase of QTc of 7-10 ms in TQT studies
- Healthy volunteer placebo controlled cross-over study
Ketoconazole increased domperidone exposure, approx threefold.
PK or PD interaction, or both?

- Domperidone alone increased QTcF by a mean of 4.2 ms
- Ketoconazole alone increased QTcF by a mean of 9.2 ms
- The combination increased QTcF by a mean of 15 ms, despite the threefold increase in domperidone exposure
c) A QTc prolongator is combined with another QTc prolongator
The combination of single dose ondansetron and droperidol (Charbit et al 2008)

Antiemetics commonly co-administered for postoperative nausea; clinical reports of QT prolongation

Healthy volunteer placebo controlled cross-over study

Both drugs on their own significantly increased QTc compared to placebo, with substantial mean increases

No PK interaction

The combination did not substantially increase QTc above droperidol alone!
Concluding questions and thoughts on QTc related DDIs

• How does the full exposure-response curves look with different QTc prolonging drugs? Do they generally have the same theoretical maximal effect in vivo, or does this vary?

• Is there a general pattern of sum QTc effects of two QTc-prolonging drugs. If so, examples imply that it may be less than additive. Why?

• hERG channel block and effects on hERG channel trafficking have been described as distinct pharmacological mechanisms causing QT-prolongation. Also, there may be different binding sites to the hERG channel. How do these interact? Are there yet other mechanisms?

• Metabolite exposure/effects must be considered.

• One or both drugs may also have anti-torsadogenic properties (effects on other cardiac ion channels), mitigating the TdP risk.

• The absolute risk increase of TdP with QT-related DDIs seems generally very difficult to ascertain. Patient-related risk factors considerably impact the absolute risk.

• ECG monitoring is recommendable on co-administration that may increase the risk.