TRIaD: A New Strategy for Drug Induced CV Risk Assessment

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AGENDA

- hERG-blockade & QT/QTc as biomarkers for drug induced proarrhythmia
  - Where the concept failed
  - Why the concept (partially) failed
  - The Ranolazine “lesson”

- TRIaD combines classical & alternate approaches
Is QT or is Proarrhythmia our Target?

- QT prolongation is only a “weak surrogate biomarker” for proarrhythmia risk
- But “it’s the only one we have” (Dr. Throckmorton, FDA)
- What we are looking for: **RARE** severe life-threatening arrhythmias
  - Which are extremely rare like TdP (1:2000-1:20000)
  - Which are no way fatal all time
  - Which can hardly be predicted
  - Which depend on transient conditions like low K-level as well as
  - Congenital LQTS/SQTS
AF, TdP, VT and Asystoly After Sotalol


2 Minutes without any heartbeat; sustained cardiac function & recovery without damage

75 year female with AF
hERG-Blockade & QT: Biomarkers of Proarrhythmia?

• Many hERG-blockers are proven drugs with proarrhythmia potential
  BUT: Verapamil is one of the strongest hERG-blockers, while proven antiarrhythmic & no proarrhythmia potential

• Amiodarone increases QT prolongation easily by >50 msec, yet it exhibits no reverse use dependency and is associated with a low risk of proarrhythmia.

• Mexitilene shows no QT/QTc prolongation, but induces TdP and proarrhythmias in 5% of patients

• Mibefradile causes T-wave changes without QT prolongation, but induced TdP and was withdrawn for observed SCD cases.
Equal QT-prolongation - Different TdP Risk: Why?

Drug-induced QT-prolongation and TdP can be dissociated in humans and in animals

Canine Model of AV-block (Verduyn et al., JACC 1997: 30:1575-1584):

<table>
<thead>
<tr>
<th>DRUG</th>
<th>QT-prolongation</th>
<th>TdP incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>D-Sotalol</td>
<td>45 ms</td>
<td>0-5%</td>
</tr>
<tr>
<td>Dofetilide</td>
<td>55 ms</td>
<td>67%</td>
</tr>
</tbody>
</table>


- ~2-5ms QT-prolongation, no TdP
- QT-prolongation is higher with low doses !!!
Why are Sotalol-induced EADs suppressed by Ranolazine in a dose-dependent manner?

- Transmural dispersion of repolarization in perfused canine left-ventricular wedge preparation does not happen-why?
Ranolazine Effect on $I_{Kr}$ and $I_{Na}$ Explains the “Miracle”

Canine LV myocyte model  

$I_{Kr}$
- has a tendency to **prolong APD** (~QT-time) and
- is blocked at IC$_{50}$ = 12 µM

$I_{Na}$
- has a tendency to **shorten APD** (~QT-time) and
- is blocked at IC$_{50}$ = 6 µM

Late $I_{Na}$ effect mitigates the $I_{Kr}$ effect in therapeutic range of 2-6 µM

Effect of outward repolarizing current is counterbalanced by inhibition of the late inward current

QT-prolongation in man exists, but is heart rate independent!

Ranolazine counteracts drugs that increase transmural dispersion and

Ranolazine does **not even increase transmural dispersion under condition of hypokalemia**!
Ranolazine suppresses EADs and Shortens AP


Fig. 3. Reversal and suppression by ranolazine of ATX-II-induced prolongation of the action potential and early afterdepolarisation (EAD), respectively, in guinea-pig isolated ventricular myocytes. Panel A: Recordings of action potentials from ventricular myocytes (a) in the absence of drug (control), (b) in the presence of 10 nM ATX-II, and (c-f) in the presence of ATX-II (10 nM) and increasing concentrations (1, 3, 10 and 30 μM) of ranolazine. Panel B: Concentration-response relationship for ranolazine to decrease action-potential duration (APD) in the presence of 10 nM ATX-II. Bars indicate the mean and SEM of measurements from 5 to 10 myocytes. Reproduced from Song et al. 2004 with permission from author and publisher.
TRlαD

- **Triangulation**
  (=prolongation of APD30-90 in canine Purkinje fiber)

- **Reverse use dependency**
  (QT prolongation dependent from heart rate)

- **Electrical Instability of the action potential and**

- **Dispersion of refractoriness**
  (=transmural dispersion of repolarization).
Transmural Dispersion of Repolarization: IKr + IKs block at cycle length 2000 canine wedge

By courtesy of Charles Antzelevich
Transmural Repolarization Wedge

baseline

Combined blockade

By courtesy of Charles Antzelevich
Prolonged QT, EADs and Transmural Dispersion of Repolarization TOGETHER Cause TdP

Drug substances which

1. cause QT prolongation
2. **AND** induce EADs
3. **AND** increase transmural dispersion

are prone to cause TdP

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**Association of EADs and increased dispersion of ventricular repolarisation with occurrence of torsade de pointes**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Induces EADs</th>
<th>Increases dispersion</th>
<th>Torsade de pointes in humans</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quinidine</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>d-Sotalol</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Terfenadine</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Cisapride</td>
<td>+</td>
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<tr>
<td>Moxifloxacin</td>
<td>+</td>
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<tr>
<td>Sodium pentobarbital</td>
<td>-</td>
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<tr>
<td>Ranolazine</td>
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*All these drugs prolong the action-potential duration and the QT interval (updated from Belardinelli et al. 2003)*. Data are from studies in canine LV wedge preparations.
Drug Candidate No QTc-Effect, but Changed T-wave

ECG from anesthetized instrumented dog

Low dose 3x therap.
High dose 10x therap.
Extreme dose 30x therap.
TRIaD Main Conclusions

"Block of hERG channel and QT interval prolongation should be considered warning signals for proarrhythmia but per se should not constitute a reason for considering a drug to be proarrhythmomic.

Conversely, the presence of TRIaD augmentation, even in the absence of QT interval prolongation, should be considered proarrhythmic until proven otherwise....

Assessment of proarrhythmic risk can be improved by considering changes in other ECG metrics, such as change in T-wave morphology and/or occurrence of U waves, time from T peak to Tend, or T-wave residuals. ..

There is no evidence to indicate that agents lacking TRIaD augmentation can be torsadogenic, extensive preapproval cardiac safety evaluation may not be called for (if absence of effects on TRIaD has been demonstrated preclinically)".
TRIaD Strategy – a Future Perspective?

The TRIaD strategy merits detailed exploration.

Possible enhancements are:

- Dan Roden’s concept of „Repolarization Reserve“
- Complementary In-Silicio models to understand mode of drug action
- FDA’s Fast Track Initiative search for new biomarkers

The challenge to our future work is:

- making drugs safer
- without deleting the promising and medically beneficial drug candidates

Literature:

Thanks for the Attention

Chateau Frontenac, Quebec, CA