Incorporating Early Assessments of Cardiovascular and CNS Safety into Early Clinical Studies

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Objectives of Early Clinical Research

1. Establish safety
   - Understanding the maximum tolerated dose or maximum feasible dose in human
   - Translation of nonclinical to clinical observations
   - Unexpected safety observations

2. Understand pharmacokinetics (dose-exposure)

3. Explore potential for efficacy
   - Clinical outcome measures
   - Biomarkers (target engagement, mechanism-of-action)
CNS Safety Assessment
Why Monitor CNS Safety?

- Early decision-making
- Critical for tolerability profile and appropriateness of patient populations
- Product differentiation
CNS Side-effects from Non-CNS Drugs

Examples:

- **Cardiovascular**
  - Beta-blockers for hypertension can result in insomnia, depression, nightmares
  - ACE inhibitors: dizziness, drowsiness, light headedness

- **Respiratory**
  - Anti-histamines. non-sedating do not cross the BBB

- **Anti-viral**
  - Non-nucleoside reverse transcriptase inhibitors, like efavirenz (Sustiva®), rilpivirine (Edurant®), can result in mood changes, anxiety, dizziness, sleep disturbance (insomnia, nightmares), and even psychosis

- **Immune modulators**

- **Metabolic disease**
Unwanted CNS Activity

- On-target, wrong tissue
  - Anti-histamines
    - Sedating: can cross BBB
    - Non-sedating: can’t cross BBB

- Off-target
  - Neurotransmitter receptors (dopamine, serotonin, GABA and acetylcholine)
  - Efanirenz (NNRTI) interacts with 5-HT<sub>2A/C</sub> receptors, serotonin & dopamine reuptake, monoamine transporter, and GABA<sub>A</sub> receptors
Alone the drugs had a minimal effect, but in combination the negative effect on reaction times was equivalent to having a blood-alcohol level of 0.1%.
Cambridge Cognition (Computerized Tests)

- Reaction Time
- Spatial Working Memory
- Rapid Visual Information Processing
- Paired Associates Learning

From Cambridge Cognition©
Clinical Trial Information System (CTIS) Profile

- **Reaction Time (RTI)**
  - Assay for mental response speeds as well as movement times and accuracy

- **Paired Associates Learning (PAL)**
  - A visual associative memory and new learning task to accurately assess episodic memory

- **Spatial Working Memory (SWM)**
  - Requires retention and manipulation of visuo-spatial information. Measures working memory and executive function

From Cambridge Cognition©
## Validity and Sensitivity

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity to Cognitive Impairment</th>
<th>Sensitivity to Cognitive Enhancement</th>
<th>Validity</th>
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<tbody>
<tr>
<td><strong>Spatial Working Memory</strong>&lt;br&gt;(SWM)</td>
<td>Tyrosine depletion in healthy subjects (d=0.42) (Harmer et al., 2001).</td>
<td>Methylphenidate in healthy subjects (d=1.51) (Elliot et al., 1997).</td>
<td>Owen et al., 1990; Manes et al., 2002; Owen et al., 1996</td>
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<tr>
<td><strong>Paired Associates Learning</strong>&lt;br&gt;(PAL)</td>
<td>Scopolamine in healthy Subjects (d=1.12) (Rusted &amp; Warburton, 1988). Rosiglitazone (no placebo) in diabetes (d=0.69) (Ryan et al., 2006).</td>
<td>Phenererine in patients with Alzheimer’s disease (d=0.46) (Greig et al., 2005).</td>
<td>Owen et al., 2002; Swainson et al., 2001; de Rover et al., 2011</td>
</tr>
<tr>
<td><strong>Reaction time (RTI)</strong></td>
<td>Clonidine in healthy subjects (d=1.52) (Jakala et al., 1999).</td>
<td>Caffeine in healthy volunteers (d=0.44) (Attwood et al., 2007).</td>
<td>Robbins, 2002</td>
</tr>
</tbody>
</table>

Published data show that drugs can improve or impair performance in these tests.

From Cambridge Cognition©
Sensitivity of Outcome Measure

Effect size's greater than 0.8 are considered to be “large” and would be expected to be clinically significant, and require serious evaluation by the clinical study team.

**Cohen (1988), Kraemer and Kupfer (2006)**
Key Properties of CTIS Profile

- **Summary**
  - Three tests included in battery covering a wide range of cognitive domains
  - Takes a little over 20 minutes to complete
  - Can be used repeatedly (especially when test sessions are well spaced out)
  - Change with age is well documented
  - Test performance correlates with real life cognitive performance
  - Tests performance can be improved or impaired by drug treatment
  - Can detect clinical significant sized effects as well as sensitive to more subtle changes
  - Effects on peripheral mechanisms have been shown to influence test performance
Cardiovascular Assessments
The Evolution of Cardiac Safety Testing

Points to Consider

1997

Joint Health Canada/FDA Concept Paper

2001

FDA & CHMP Adopt E14

2003

Health Canada Adopts E14

2005

preDiCT Project begins

2007

E14 Q&A

2009

IRT Started

2011

ARITMO Project begins

2013

E14 Q&A revised

2015

preDiCT Project

ARITMO Project

Health Canada Concept Paper

ICH issues S7B and E14 Guidance
Cases of Torsades de Pointes

Annual number of spontaneous reports of Torsade de Pointes received by the US FDA Adverse Event Reporting System, Stockbridge et al. Drug Safety 2013;36:167-182
Current Regulatory Guidance (Nonclinical)

- ICH S7A (Safety Pharmacology)
  - Cardiovascular system
    - Core battery: blood pressure, heart rate, ECG
    - Follow-up: cardiac output, ventricular contractility, vascular resistance
- ICH S7B (QT prolongation)
  - Ikr (hERG) assay
  - In vivo (telemetry) QT assessment
  - Chemical/pharmacological class
  - Integrative risk assessment
ICH E14 (QT/QTc prolongation and proarrhythmic potential)
  - Specifies Thorough QT/QTc study
    - Threshold for regulatory concern: 5 ms change in QTc
    - Typically done in healthy subjects
    - Positive control (often moxifloxacin)

E14 Questions and Answers (2008)
  - Provided clarifications
    - Positive control to establish assay sensitivity (lower bound of one-sided 95% CI must be above 0 ms)
    - Who should read ECGs (must be blinded, cardiologist over-read acceptable)
Current Debate

- Does the TQT truly predict a compound’s proarrhythmia potential?
- There have been tremendous advancements in both pre-clinical and early clinical monitoring of arrhythmia potential since 2005. How does this:
  - Change proarrhythmia evaluation pre-clinically and/or clinically?
  - Change the need for a TQT?
- What has been the impact of ICH E14 and S7B on drug development? Is it worth the cost?
- What does a positive TQT really mean?
Relationship of QT Prolongation and Human Risk

- Cardiac Arrest
- Ventricular Fibrillation
  - Ventricular Arrhythmia
    - Torsades de Pointes
- Cardiac Action Potential:
  - Delayed Repolarization
- QT Prolongation
  - Early After Depolarizations

Is there an Alternative to Thorough QT Studies?
Increase Nonclinical Testing

- Comprehensive In vitro Proarrhythmia Assay (CiPA) Initiative
  - Ion channels
    - Perform comprehensive tests (hERG plus 3 to 6 additional cardiac channels)
  - Stem cell-derived human cardiomyocytes
  - In silico modeling
- Result: update ICH S7B
Early Clinical Cardiac Safety Evaluation

Proposal:

- Include intense ECG monitoring to early Single Ascending Dose (SAD) and Multi Ascending Dose (MAD) studies
  - Pool data from different dose levels to evaluate concentration response relationship
  - Typically during SAD and MAD studies the highest doses are given allowing for better concentration response modeling
Early Clinical Cardiac Safety Testing

- Consortium for Innovation and Quality in Pharmaceutical Development/Cardiac Safety Research Consortium (IQ/CSRC)
  - Look at six marketed drugs, 5 positive QT signal and 1 negative control
  - Two doses: 10-12 ms and 15-20 ms
    - Ondansetron, dofetilide, quinine, dolasetron, moxifloxacin
    - Levocetirizine (negative control)
  - SAD-like study

- QT assessment criteria: The upper bound of the two-sided 90% confidence interval (CI) of the projected placebo-corrected delta QTcF is above 10 ms at the observed peak plasma level of the drug

- Sensitivity and specificity of measuring QT prolongation
- Concern over potential false negatives (regulators) and false positives (sponsor)
IQ-CSRC Study

- 3 period, randomized, placebo-controlled study
- Incomplete block design used
  - Each study drug administered to 9 subjects and placebo to 6 (total n=20)
- Continuous 12-lead ECGs with replicate ECGs extracted
- Exposure response analysis performed
  - Evaluate relationship between plasma concentration and placebo corrected, change-from-baseline QTc ($\Delta\Delta QTc$)
- “QT positive” if the UB of the 2-sided 90% CI of the predicted placebo-corrected $\Delta QTcF$ is above 10 ms at the observed geometric mean $C_{\text{max}}$ of the lower dose of the studied drugs

Darpo et al. (2014) *Ann Noninvasive Electrocardiol* 19, 70-81
IQ-CSRC: Pharmacokinetics and QT Data

IQ-CSRC Study: Exposure-response Results

Implications of IQ-CSRC Study

- No positive control in SAD
  - Reassurance against false negatives
  - Risk is small when exposure-response analysis is applied and offset by wide range of plasma concentrations
- Quality test metrics
  - HR stability within time points
  - Reproducible QT/RR curvature
  - Within and between subject variability of QT
  - Time course of QT adaptation to changes in HR
- Study was SAD-like, not exactly like a dose-escalation study
- Group sizes were larger than “typical” SAD
Future Directions

- Need further replication of the IQ-CSRC study
- Pharmacokinetics will drive study design
  - Pronounced accumulation on multi-dosing?
  - Sufficiently high plasma concentration of parent and metabolites?
- Could TQT waiver be obtained?
References

- Darpo et al. (2015) Results from the IQ-CSRC prospective study support replacement of the thorough QT study by QT assessment in the early clinical phase. *Clin Pharmacol Ther* 97, 326-335
Questions?
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