Investigating the Ethnic Differences between the Effects of Moxifloxacin on Cardiac Conduction in Japanese and Caucasians

Jorg Taubel MD FFPM
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Overview

1. Is there literature suggesting ethnic differences in QTc responses to medicines?
2. The results from our own work so far (published and pending publication)
3. Outlook and further work proposed/planned
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Genetic Polymorphism

1. PK effects
2. PD effects
• There are significant inter-ethnic differences in the frequency of variant alleles of genes (e.g. CYP2D6, CYP2C19, CYP2C9) resulting in inter-ethnic differences in metabolism of their substrates.

• Highly polymorphic CYP2D6 and the frequency of variant alleles of CYP2D6 that result in impaired drug metabolism (increased plasma concentrations) is higher among white Caucasians compared with their Oriental counterparts.

• There are marked inter-ethnic differences in the frequency of variant alleles of genes, encoding for cardiac ion channels, with some alleles being population-specific. The frequency of variant KCNH2 alleles that results in sensitivity to drug-induced QT interval prolongation is higher among White Caucasians.

Shah RR.
Drug-induced QT interval prolongation: does ethnicity of the thorough QT study population matter?

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Published FDA Data on Moxifloxacin

- Pooled analysis of 20 TQT studies
- A subset of 60 Asian (Indian, Japanese and Chinese) subjects from 4 studies contributing 3, 9, 20 and 28 subjects each was compared to 788 Caucasian subjects
- $C_{\text{max}}$ exposure in Asians was +6% compared to Caucasians
- No significant race effects were detected

Figure 1. Summary ΔΔQTcF versus time plots for the 20 pooled TQT studies divided by ... race category (...Caucasian [n = 788], solid, circles; black [n = 105], dotted, plus symbols; Asian [n = 72], dash-dot, diamonds). ... quantile means ± 90% confidence interval. ...

Quinidine in American and Korean infusion of quinidine (4 mg kg\(^{-1}\)) for 20 min

<table>
<thead>
<tr>
<th>N</th>
<th>Korean</th>
<th>Caucasian</th>
</tr>
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<tbody>
<tr>
<td>Male</td>
<td>12</td>
<td>7</td>
</tr>
<tr>
<td>Female</td>
<td>12</td>
<td>6</td>
</tr>
<tr>
<td>Total</td>
<td>24</td>
<td>13</td>
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Significant QTc prolongation \(~75-100\text{ms}\)

Flockhart DA et al.
Possible interethnic differences in quinidine-induced QT prolongation between healthy Caucasian and Korean subjects.
PK-PD Study in Korean ○ and Caucasian ●

Limitations:
- QTcB
- HR effects not described (HR effect, use dependent block)
- Study in two sites
- No ECG baseline day/baselines >450 msec
- Placebo data not presented
- Paper ECG, different equipment in sites
- ECG over-reading

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# Investigating Ethnic differences

<table>
<thead>
<tr>
<th>QT studies involving Japanese</th>
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<tbody>
<tr>
<td>Moxifloxacin</td>
</tr>
<tr>
<td>Antipsychotic (marketed)</td>
</tr>
<tr>
<td>H1 Antagonist (marketed)</td>
</tr>
<tr>
<td>Levofloxacin</td>
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<table>
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<tr>
<th>QT studies investigating physiological effects involving Japanese</th>
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<tbody>
<tr>
<td>Insulin</td>
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<tr>
<td>C-Peptide</td>
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<td>Glucose</td>
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With reasonable sample sizes, moxifloxacin control and high precision ECG acquisition *and* high precision measurements all of these studies showed either no difference between ethnicities or minuscule differences which in all instances were not statistically significant. That does not mean clinically differences cannot exist, but we certainly have not seen any evidence for differences in sensitivity so far.
Levofloxacin post hoc analysis

- Japanese subjects show the extremes of QTc shortening/lengthening
- Caucasians have the highest plasma concentrations
- The slope indicates the QTc prolonging properties of Levofloxacin
- The slope for the Japanese subjects is flatter, that of the Caucasians steeper
- The confidence intervals overlap
- No significant differences

Sugiyama et al.
Br J Clin Pharmacol 2011

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**400mg oral Moxifloxacin after a meal**

Design: 4-way cross-over studies, single dose. Study 1: N= 42 /Study 2: N= 32
All subjects received 400mg oral moxifloxacin 10 minutes after completing a breakfast Placebo baseline day preceded all treatment days; oral placebo after breakfast only

RED: Japanese, BLACK: Caucasian

**STUDY 1 [N=42]**

Note the -- largely PK driven -- delay in QTc response.
400mg oral Moxifloxacin after a meal

Concentration effect modelling (CEM):

STUDY 2 [N=32]

Note we found a reverse relationship in fasting condition in Study 2 (published)

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Combining TQT with Ethnic PK Bridging

• Where Ethnic PK Bridging is intended and the moxifloxacin arm in a “TQT” study is *not* mandatory: This may be easily combined with thorough ECG assessments during that study to
  – Provide further PK-PD data on cardiac safety
  – Allow head-on ethnic comparisons in the same study
  – Can be used in a combined analysis where a TQT study has already been done in another ethnicity

• Two studies in one -- save time and cost.

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**TQT in Japanese PK Bridging**

**Design:**
SAD study in 3 cohorts of N=9 (6 active, 3 placebo)
Placebo baseline day preceding all treatment days.

**Graph:**
- 5 scatter plots showing data points for dQCcF corrected for time.
- 2 line graphs showing dQTcf over time.
- Vertical lines at 2, 4, 6, 8, 10, and 12 hours.

**PK-PD Analysis**

**Time Course Analysis**
(meal effect confirming ECG sensitivity)

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**Food produces a consistent QT effect**

- Smart + simple method
- Physiological response
- Reliable and reproducible
- Described by others

1. Shortening of the QT interval after food can be used to demonstrate assay sensitivity in thorough QT studies
2. Insulin at normal physiological levels does not prolong QTc interval in thorough QT studies performed in healthy volunteers
3. Concentration-effect modelling based on change from baseline to assess the prolonging effect of drugs on QTc together with an estimate of the circadian time course.
4. Acute hyperglycaemia disturbs cardiac repolarization in type 1 diabetes.

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Physiological Effects

The effect is similar with different types of meals; although a fatty meal (containing less carbohydrate) leads to a slightly smaller effect (AUC).

Taubel J et al.

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high carbohydrate breakfast on QTcF

2-4 hours after meal
Glucose: J>C
C-Peptide: J>C (lower at start)
QTcF shortening: J<C

<table>
<thead>
<tr>
<th></th>
<th>Japanese</th>
<th>Caucasian</th>
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<tr>
<td>Emax</td>
<td>1 hour</td>
<td>3 hours</td>
</tr>
<tr>
<td>mean change QTcF [90%CI] msec</td>
<td>-5.8 [-9.4, -2.3]</td>
<td>-12.2 [-16.0, -8.4]</td>
</tr>
</tbody>
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Meal effect on ECG published by others

Results are simple to interpret

For the second meal, *no samples* were taken at appropriate time points:

Whatever the effect of the second meal, it was quite simply missed.


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Conclusions

1. Currently there is no evidence for clinically significant ethnic differences in QTc response for a number of medicines so far

2. Similarity in physiological response to a meal, but c-peptide PK-PD may be different?

3. We can further improve our studies by enhancing specificity and reducing cost.
   - For example by combining PK Bridging PK studies with ECG assessments
I thank my co-workers for their contributions:

- Dr Georg Ferber (statistics)
- Dr Ulrike Lorch (clinical work)
- Professor John Camm (encouragement!)
Thank you

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