Effect of Levofloxacin on QT/QTc Assessed in Healthy Japanese and Caucasian Subjects

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• Description of studies and methods
• Presentation of our research results
• Discussion of results and literature
• Conclusions
Background (1)

• Little is known about racial differences of medication induced QTc changes
• Genetic factors relating to inter-individual variations in the length of the QT interval are well recognized
• It is thus perceivable that different human populations may respond differently to medicines
• The results of two published studies using Levofloxacin in Japanese\(^1\) and Caucasian\(^2\) subjects were pooled in a post hoc analysis to investigate the similarity of dose-effect responses in Japanese and Caucasian healthy volunteers


• Levofloxacin is a fluoroquinolone antibiotic
• Fluoroquinolones inhibit HERG K⁺ channels
• Levofloxacin is a less potent inhibitor than Moxifloxacin in-vitro¹
• In the case of Levofloxacin inhibition occurs at levels much greater than those observed clinically¹

<table>
<thead>
<tr>
<th></th>
<th>Sugiyama et al.</th>
<th>Taubel et al.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site:</td>
<td>Kitasato University, Tokyo</td>
<td>St George’s University, London</td>
</tr>
<tr>
<td>Design:</td>
<td>2-way cross-over trial</td>
<td>4-way cross over trial</td>
</tr>
<tr>
<td>IMP:</td>
<td>Levofloxacin 500mg i.v.</td>
<td>Levofloxacin 1g and 1.5g p.o.</td>
</tr>
<tr>
<td>Controls:</td>
<td>Placebo</td>
<td>Placebo Moxifloxacin 400mg oral s.d.</td>
</tr>
<tr>
<td>Subjects:</td>
<td>48</td>
<td>64</td>
</tr>
<tr>
<td></td>
<td>24 young (20-45), 12M/12F</td>
<td>mean age 29 years</td>
</tr>
<tr>
<td></td>
<td>24 elderly (65-79, 12M/12F</td>
<td>34M/30F</td>
</tr>
<tr>
<td>Baseline Correction:</td>
<td>Single ECG baseline for both periods</td>
<td>time matched ECG baseline day preceding each of the periods</td>
</tr>
</tbody>
</table>
• Triplicate 12-lead bed-side ECG were recorded
• ECG were analysed automatically and manually over-read (manual adjudication) using a threshold method in different sites
• Intervals were extracted and QTcF calculated
• The Caucasian study established a new baseline for each period of the crossover, whereas the Japanese study used a common baseline for both periods. Therefore the baseline was not used in this analysis.
“E14” Analysis Results (dose response)

<table>
<thead>
<tr>
<th></th>
<th>Sugiyama et al.</th>
<th>Taubel et al.</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔΔQTcF (CI*) [ms]</td>
<td>3.4 (5.2) following 500mg i.v.</td>
<td>4.7 (7.0) following 1000mg p.o. 7.1 (9.1) following 1500mg p.o. (dose proportional response)</td>
</tr>
</tbody>
</table>

* upper bound of one-sided 95% confidence interval

Assuming a bioavailability of 100%, a linear dose response in Japanese comparable to Caucasians (same slope) would lead to a 6.8 and 10.2 ms prolongation of QTc at 1000mg and 1500mg doses respectively.

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Methods: concentration effect analysis

- the Levofloxacin pk data from both trials and the numerical ECG data from the Japanese dataset were transferred to London for a pooled analysis
- to make the two datasets comparable a concentration-response model was fitted
- the predicted effect on QTcF at the geometric mean $C_{\text{max}}$ of the two oral doses was calculated based on the primary model for each race together with a two-sided 95 % confidence interval. The same was done for the difference of these effects between races.
### Pharmacokinetics

#### Table 1 Pharmacokinetic parameters of levofloxacin in Caucasian subjects [Mean ± standard deviation]

<table>
<thead>
<tr>
<th>Dose</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; [µg/mL] (arithmetic mean)</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; [µg/mL] (geometric mean)</th>
<th>AUC&lt;sub&gt;24&lt;/sub&gt; [µg.h/mL]</th>
</tr>
</thead>
<tbody>
<tr>
<td>500mg i.v.</td>
<td>10.2±2.3</td>
<td>10.0±1.3</td>
<td>66.3±14.8</td>
</tr>
<tr>
<td>1000mg p.o.</td>
<td>9.6±2.1</td>
<td>9.3±1.2</td>
<td>99±17</td>
</tr>
<tr>
<td>1500mg p.o.</td>
<td>13±2.1</td>
<td>12.5±1.2</td>
<td>150±26</td>
</tr>
</tbody>
</table>

- The absolute bioavailability of oral Levofloxacin has been reported as >99%<sup>1</sup>

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The pk data from the three studies does not fully reconcile; note Sugiyama and Chien are both 500mg i.v. doses given over 60 minutes. Accounting for weight the Cmax results are about 50% out and the AUC data about 20%
Japanese subjects show the extremes of QTc shortening/lengthening

Caucasians have the highest plasma concentrations

The (linear) 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
Results

Predicted QTcF slope and double sided 95% confidence interval
## Results

<table>
<thead>
<tr>
<th>Model</th>
<th>AIC</th>
<th>BIC</th>
<th>Effect</th>
<th>Estimate</th>
<th>95% Confidence Intervals</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Lower</td>
<td>Upper</td>
<td></td>
</tr>
<tr>
<td>M1</td>
<td>12977.6</td>
<td>13044.6</td>
<td>Offset.Jap.f</td>
<td>-0.462</td>
<td>-2.679  1.755</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Offset.Jap.c</td>
<td>-0.287</td>
<td>-2.501  1.926</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Offset.Cauc.f</td>
<td>-1.286</td>
<td>-4.879  2.306</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Offset.Cauc.m</td>
<td>-1.111</td>
<td>-2.839  0.616</td>
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<td></td>
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<td></td>
<td>Slope.J.f</td>
<td>0.392</td>
<td>0.150  0.635</td>
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<td>Slope.J.m</td>
<td>0.367</td>
<td>0.059  0.675</td>
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<td>Slope.Cauc.f</td>
<td>0.404</td>
<td>0.246  0.562</td>
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<td>Slope.Cauc.m</td>
<td>0.594</td>
<td>0.429  0.758</td>
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<td>Slope.diff.Jap</td>
<td>0.025</td>
<td>-0.367  0.417</td>
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<td>Slope.diff.Cauc</td>
<td>-0.190</td>
<td>-0.418  0.038</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Slope.diff.female</td>
<td>-0.012</td>
<td>-0.301  0.278</td>
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<tr>
<td></td>
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<td>Slope.diff.male</td>
<td>-0.227</td>
<td>-0.576  0.123</td>
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<tr>
<td>M2</td>
<td>12979.6</td>
<td>13024.6</td>
<td>Slope.Jap.f</td>
<td>0.373</td>
<td>0.148  0.599</td>
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<tr>
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<td></td>
<td>Slope.Cauc.f</td>
<td>0.418</td>
<td>0.262  0.573</td>
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<tr>
<td></td>
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<td></td>
<td>Slope.Cauc.m</td>
<td>0.570</td>
<td>0.410  0.731</td>
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<td></td>
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<td>Slope.diff.Jap</td>
<td>-0.023</td>
<td>-0.382  0.336</td>
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<td></td>
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<td>Slope.diff.Cauc</td>
<td>0.153</td>
<td>-0.071  0.376</td>
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<td></td>
<td></td>
<td></td>
<td>Slope.diff.female</td>
<td>-0.044</td>
<td>-0.318  0.230</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Slope.diff.male</td>
<td>-0.220</td>
<td>-0.542  0.102</td>
</tr>
</tbody>
</table>

### Concentration-Response Modelling in Japanese and Caucasian Subjects

Effects of plasma concentrations of Levofloxacin on change of QTcF from time matched placebo Analysis by Gender

- **M1:** Fixed intercept and slopes, Random: Intercept and slope
- **M2:** No fixed intercept, Random: Intercept and slope

Overall, inclusion of gender into the analysis does not show any significant effects.
Effect of plasma concentrations of Levofloxacin on change of QTcF from time matched placebo.

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Limitations of this Study

• This is a post-hoc analysis
• The variable of interest is race
• The results shown may be influenced, masked, distorted or reversed by other variables e.g.:
  – Different sites
  – Different study designs
  – Different doses/drug administration
Quinidine

- Study in 24 Korean (12M/12F) and 13 Caucasian (7M/6F)
- Caucasian subjects were found to be more sensitive to quinidine induced QTcB prolongation, particularly females
- Two study sites: the authors qualify the findings in their paper stating that they can not rule out various environmental factors

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
- Cmax 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. …

Conclusions

However...
• Investigator lead Caucasian and Japanese bridging study where race is the only variable, to assess (amongst others):

1. racial differences in moxifloxacin response
2. effects of different types of food on the QTc interval
3. effects of food on the moxifloxacin response
4. effect of an euglycaemic insulin clamp on QTc

Interim results in 11 Caucasian and 13 Japanese only (First 2 Cohorts); not QC checked
Please note:

The full data will be presented at the upcoming JSCPT, BPS and ASCPT meetings; interested parties can contact the author to discuss specific questions related to our research.

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Conclusions

• Data from our secondary analysis suggests that Japanese and Caucasian healthy volunteers show a similar plasma concentration -- QTcF effect response when administered Levofloxacin 0.5-1g

• A non significant difference in the concentration-effect slope suggests that Japanese would be less sensitive to the HERG channel blocking properties of Levofloxacin
Conclusions

• Data from literature suggests that the same could be true for Moxifloxacin (in a mixed group of Asians) and Quinolone (in Koreans)

• However a recent bridging study (which excluded other variables than race) showed the opposite effect for a 400mg single dose of Moxifloxacin: the data suggests that Japanese could be more sensitive to the HERG channel blocking properties of Moxifloxacin
Conclusions

- More work is needed to gather further data
- We recommend a bridging study approach to TQT studies
• Professor Atsushi Sugiyama
• Daiichi Sankyo
• Professor John Camm and the cardiologists at the Department of Cardiovascular Sciences at St Georges
• Dr Ulrike Lorch and her team at Richmond
• Dr Georg Ferber
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