PKPD-Modelling of QT Prolongation Following Deliberate Self-Poisonings with Citalopram

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PKPD studies in clinical toxicology

- No controlled studies
  - Uncertainty in dosing history
- Co-ingested drugs
- Decontamination procedures
  - Activated charcoal
  - Vomiting
- Sparse sampling
  - Few samples in absorption phase
Analysing PK and PD data from overdoses

- Population PKPD analysis
- Fully Bayesian methodology
  - Prior information

\[ p(\theta | y) \propto p(\theta) \cdot p(y | \theta) \]

- Uncertainty in dose and time
Citalopram in overdose

- Antidepressant – SSRI
- QT prolongation in a larger frequency than other SSRIs
  (Isbister et al, 2004)
- Documented cases of Torsade de Pointes (TdP)
  (Tarabar et al, 2003; Meuleman et al, 2001)
- Several fatal cases described
  (Öström et al, 1996; Jonasson and Saldeen, 2002)
QT-RR

Fossa et al. J Pharmacol Exp Ther, 2005
Aim

- To develop a PKPD-model describing the time course of QT prolongation for citalopram
- To evaluate the effect of charcoal administration on the relative risk of TdP after citalopram overdose
Data set

- 53 patients who had taken citalopram in an overdose event
  - 63 events
  - 36 females (68%)
  - 13-72 years (median 30 years)
  - Reported dose: 20-1700 mg (1 – 85 tablets)
  - Single dose activated charcoal on 17 events (0.5-4 hours after the overdose)
  - 39 patients were taking citalopram therapeutically
  - No case of TdP
## Veracity grade of dosing history

<table>
<thead>
<tr>
<th>Veracity grade</th>
<th>Description</th>
<th># of events</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Excellent history</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>Good history</td>
<td>21</td>
</tr>
<tr>
<td>2</td>
<td>Less reliable history</td>
<td>15</td>
</tr>
<tr>
<td>3</td>
<td>Poor history</td>
<td>27</td>
</tr>
<tr>
<td>4</td>
<td>Very poor history</td>
<td>0</td>
</tr>
</tbody>
</table>
Dose-normalised (30 mg) concentrations vs. time (n=189)
Observed QT-RR intervals

- 167 QT and RR combinations
  - 33 combinations at “increased risk”
Data analysis

- WinBUGS v. 1.4

- Prior information
  - PK Informative
    - 14 PK studies on citalopram taken in therapeutic doses
  - PD Low-information
    - Biologically plausible
Final PK model

Uncertainty in dose \sim \text{veracity grade}

- Reduced F by 22%
- Increased CL by 72%

Uncertainty in time of ingestion

Activated charcoal

1-compartment
Dose-dependent clearance? Interactions with co-ingestants?

- Metabolised by CYP3A4 and/or CYP2C19

- CL/F (L/h) vs. Dose (mg)
  - No co-ingestant
  - Co-ingestant(s)
Simulation study
Bias in PK parameters in 30 data sets with the same "design"
PKPD model of QT interval prolongation

\[ QT_{ij} = QT_{C_{ij}} \cdot RR_{ij}^{\alpha_i} \]

\[ QT_{C_{ij}} = QT_{C_{i,0}} + \text{Slope}_i \cdot C_{e_{ij}} + \Delta QT_{C_{i,\text{co-ingestant drugs}}} \]

- \( t_{eq} = 1.4 \) h
- \( \alpha = 0.36 \)
- \( \text{Slope} = 40 \text{ L} \cdot \text{ms/mg} \)
- \( QT_{C_{i,0}} \)
  - 9 ms higher in women
  - Increased with age
- \( \Delta QT_{C_{i,\text{co-ingestant drugs}}} \)
  - < 5 ms
Simulation of probability for risk of TdP from PKPD model

- 2000 patients
  - 10 dose levels:
    5-90 x DDD (Defined Daily Dose; 20 mg)
- Median of observed RR intervals (760 ms)
  ⇒ QT interval with increased risk of TdP (447 ms)
Probability of risk for TdP with and without activated charcoal

RR = 80 bpm (= 760 ms)

Without charcoal

With charcoal
Relative reduction in hazard/risk for TdP by charcoal
Conclusions

- Informative priors and veracity judgements on dosing history could be used for developing a PKPD model from overdose data.
- Activated charcoal reduced F and increased CL after citalopram overdoses.
- QT prolongation was delayed relative to $C_{max}$ of citalopram.
- Administration of activated charcoal reduced the risk for TdP by approximately 60%.
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