PBPK modelling to derisk DDI: a case study

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Background

Setting the scene

Therapeutic area: epilepsy

Brivaracetam (Briviact®)
- Antiepileptic (AED) drug recently approved.
- Recommended doses: 100 & 200 mg/day
- Bioavailability ~ 100%
- Linear pharmacokinetics
- In vitro, Brivaracetam had no effect on CYP1A2, 2A6, 2B6, 2C8, 2C9, 2D6 and 3A4 but inhibited 2C19 (competitive inhibition)
- No time dependant inhibition (TDI)

Phenytoin
- Widely prescribed anticonvulsivant
- Small therapeutic index
- Potential severe adverse effects
- Elimination through CYP2C9 & CYP2C19
- Caution in CYP2C9/2C19 poor metabolizers and when coadministered with CYP2C9/2C19 inhibitors

Brivaracetam is likely to be co-administered with Phenytoin
**Background**

Brivaracetam is likely to be co-administered with Phenytoin

*In vitro* results

![Graph showing percent inhibition of CYP activities](image)

- Concentration = $50 \times \text{Cmax}_u = 650 \, \mu\text{M}$
- Competitive inhibition – $K_i = 314 \, \mu\text{M}$
Background

Brivaracetam is likely to be co-administered with Phenytoin

*In vivo study*

- 19 epileptic patients stable on phenytoin monotherapy
- Repeated administrations of brivaracetam at 400 mg/day (200 mg bid)

<table>
<thead>
<tr>
<th></th>
<th>$C_{\text{max}}$ ($\mu$g/mL)</th>
<th>$\text{AUC}_{\tau}$ ($\mu$g.h/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PHE</td>
<td>16.9 (37.5)</td>
<td>252 (54.8)</td>
</tr>
<tr>
<td>PHE (with BRV)</td>
<td>20.7 (38.1)</td>
<td>306 (42.6)</td>
</tr>
</tbody>
</table>

On average, both $C_{\text{max}}$ and $\text{AUC}_{\tau}$ of phenytoin were increased by 20 %

- modest amplitude
- non-approved dose
- difficult to distinguish from background variability

**BUT** notice in the US/EU labeling + phenytoin plasma monitoring (US)
And so what?...

What could we expect at brivaracetam therapeutic doses?

- Brivaracetam
  - *In vitro data*
  - *In vivo studies*

- Brivaracetam + Phenytoin
  - *In vivo study at supratherapeutic dose*

- Phenytoin
  - Literature
  - *In vivo studies*

PBPK modelling

- Brivaracetam + Phenytoin
  - *Therapeutic doses*
Modelling strategy

MODEL BUILDING

Brivaracetam
In house in vivo and in vitro data

Phenytoin
Simcyp compound file

MODEL QUALIFICATION

Brivaracetam
FIM single PO doses + Repeated administration at therapeutic doses

Phenytoin
Dedicated publications

POPULATION
Healthy volunteers
N = 250
Modelling results / qualification

Brivaracetam – single oral administration

- 10 mg
- 50 mg
- 100 mg
## Modelling results / qualification

### Brivaracetam – single oral administration

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>PREDICTED</th>
<th>OBSERVED</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cmax (ng/ml)</td>
<td>AUC (ng.h/ml)</td>
</tr>
<tr>
<td>10 mg</td>
<td>217 (29.4)</td>
<td>3059 (36.4)</td>
</tr>
<tr>
<td>50 mg</td>
<td>1084 (29.4)</td>
<td>15297 (36.4)</td>
</tr>
<tr>
<td>75 mg</td>
<td>1626 (29.4)</td>
<td>22946 (36.4)</td>
</tr>
<tr>
<td>100 mg</td>
<td>2168 (29.4)</td>
<td>30594 (36.4)</td>
</tr>
</tbody>
</table>

- simulated profiles comparable to the clinical data for all doses
- predicted geometric mean Cmax and AUC within 1.25-fold of the observed data
Modelling results / qualification

Brivaracetam – repeated oral administration

100 mg – day 1

100 mg bid – day 14
Modelling results / qualification

Brivaracetam – repeated oral administration

<table>
<thead>
<tr>
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<th>PREDICTED</th>
<th>OBSERVED</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cmax (ng/ml)</td>
<td>AUC (ng.h/ml)</td>
</tr>
<tr>
<td>Day 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2170 (27.0)</td>
<td>24725 (24.8)</td>
</tr>
<tr>
<td>Day 14</td>
<td>3726 (25.9)</td>
<td>31898 (34.7)</td>
</tr>
</tbody>
</table>

- simulated profiles comparable to the clinical data for all doses
- predicted geometric mean Cmax and AUC within 1.25-fold of the observed data
Modelling results / qualification

Phenytoin – repeated oral administration

300 mg once a day
Modelling results / qualification

Phenytoin – CYP2C19 contribution

300 mg once a day and ticlopidine (250 mg bid)

➤ **Simulations:**
  • phenytoin \( C_{\text{min}} \) increase by 74 %

➤ **Observations:**
  • 2 individuals showing \( C_{\text{min}} \) increasing by 70 – 80 %
  • 6 individuals with a dose adjustment corresponding to an 80% decrease
Modelling results / qualification

Brivaracetam (400 mg) & Phenytoin

- Brivaracetam: 100 mg BID for 3 days followed by 200 mg BID for 3 weeks
Modelling results / qualification

Brivaracetam (400 mg) & Phenytoin

- Brivaracetam: 100 mg BID for 3 days followed by 200 mg BID for 3 weeks
- Mean concentration of Phenytoin (alone) in the target range of 7-23 µg/mL
Modelling results / qualification

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Ki = 314 µM → simulations did not show any effect on the phenytoin pharmacokinetics
Modelling results / qualification

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Ki = 22 µM → simulations did show an effect on the phenytoin pharmacokinetics
Modelling results / qualification

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<thead>
<tr>
<th></th>
<th>Observed</th>
<th>Predicted</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cmax (µg/ml)</td>
<td>Tmax (h)</td>
</tr>
<tr>
<td>Without BRV</td>
<td>16.9</td>
<td>4.6</td>
</tr>
<tr>
<td>With BRV 200 mg</td>
<td>20.7</td>
<td>4.7</td>
</tr>
<tr>
<td>BID</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ratio</td>
<td>1.22</td>
<td>1.21</td>
</tr>
</tbody>
</table>

Ki = 22 µM → simulations did show an effect on the phenytoin pharmacokinetics
Modelling results / qualification

Brivaracetam (400 mg) & Phenytoin

- Brivaracetam: 100 mg BID for 3 days followed by 200 mg BID for 3 weeks
- Mean concentration of Phenytoin (alone) in the target range of 7-23 µg/mL
- Ki from 314 to 22 µM to accurately predict the DDI...

- This finding is not unique: fluvoxamine, topiramate, imipramine, ...
- Ticlopidine and felbamate: very few examples with good IVIVE for DDI prediction with phenytoin
Modelling application

### Brivaracetam (200 mg) & Phenytoin

- Brivaracetam: 100 mg BID starting on day 11 for 3 weeks
- Mean concentration of Phenytoin (alone) in the target range of 7-23 µg/mL
- Ki of Brivaracetam on CYP2C19 → 22 µM
Conclusions

- PBPK modelling allowed both model building and model qualification
- In vivo data allowed the calculation of an in vivo Ki
- Sensitivity analysis
- The simulations illustrate that the highest recommended brivaracetam dosage of 100mg BID is expected to be devoid of significant risks of interaction with phenytoin
Thanks!

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