Pharmacokinetics using a Rate Dependent Extraction Model

The Influence of Body Composition on Ethanol

Dosing and observations
Subjects consumed 40% ethanol v/v vodka drinks over 30 minutes on two occasions with sequence randomized mixed-doses calculated using predicted body water based on TBW, height, and sex to achieve a target peak blood ethanol concentration of 650 mg/dL and 1150 mg/dL.

- 6025 breath sample measurements were obtained from 108 subjects studied on 2 occasions.
- Breath alcohol concentration was converted into blood alcohol concentration (BAC) by assuming a value for portal vein blood flow (Chv) and for hepatic flow using the gut with subsequent first order absorption (Chaplin, 2005).

Methods

Pharmacokinetic model
- A semi-mechanistic rate dependent extraction model with zero-order input to the gut with subsequent first order absorption was used to describe the data.
- The change of hepatic first pass extraction ratio with absorption rate was accounted for by assuming a value for portal vein blood flow (Gpv) [4].
- Predicted concentration in the hepatic vein (Chv) was used as the concentration that drives mixed-order elimination.
- Hepatic mixed-order (VM, Km) first order (CLFO) and non-hepatic first order elimination (CLNH) processes were evaluated with (CLFO, CLNH) and without rate dependent extraction (simple mixed order plus CLFO).
- Intrinsic hepatic clearance (CLi) was predicted by solving a quadratic function [5].

Estimation and model selection
- Data were analyzed using NONMEM 7.3.0 (ADVAN13NSIG=3, SIGL=9, TOL=9). Between subject variability (BSV) and between occasion variability (BOV) were tested on all parameters.
- The likelihood of censored observations was predicted using the last observed BEC as the "lower limit of quantitation" and Beal’s M3 [4] when BOV worsened by 26.2% and worsened by 25.5% when BAC worsened by 26.2%.
- Model selection was based on changes in objective function value (OFV).

Results and Conclusions
- OFV improved by 362 with rate dependent extraction compared to simple mixed order plus CLFO.
- OFV worsened by 26.2 when Gpv predicted with TBW compared to FFM.
- OFV worsened by 177.9 when V predicted with TBW compared to NFM.
- A rate dependent extraction model improves model fitting compared with a simple mixed order model.
- Fat free mass was the best size descriptor for Gpv.
- Normal fat mass was the best size descriptor for V and total body weight for maximum elimination rate (VM).
- Predicted variability is greater than original observations compared with a fit based on simulated observations using Pred Corrected VPC.

Bootstrap Parameter Estimates

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Units</th>
<th>Bootstrap Estimate (RSE%)</th>
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<th>Bootstrap Estimate (RSE%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zero order input</td>
<td>h</td>
<td>0.301 (14.7%)</td>
<td>0.238 (84.3%)</td>
<td>0.492 (14%)</td>
<td>0.492 (14%)</td>
</tr>
<tr>
<td>First order absorption from oral</td>
<td>L/h</td>
<td>8.83 (7.7%)</td>
<td>7.10 (7.7%)</td>
<td>1.11 (113%)</td>
<td>1.11 (113%)</td>
</tr>
<tr>
<td>Volume of distribution</td>
<td>L/70kg</td>
<td>38.6 (7.5%)</td>
<td>35.5 (45.0%)</td>
<td>0.091 (23%)</td>
<td>0.149 (23%)</td>
</tr>
<tr>
<td>Est. Elim Rate</td>
<td>NFM</td>
<td>15.8 (12%)</td>
<td>11.2 (188)</td>
<td>0.258 (19%)</td>
<td>0.309 (14%)</td>
</tr>
<tr>
<td>Conc at 50% VM</td>
<td>mg/L</td>
<td>62.5 (25%)</td>
<td>45.7 (294)</td>
<td>1.22 (165)</td>
<td>1.40 (198)</td>
</tr>
<tr>
<td>Gpv</td>
<td></td>
<td>53.2 FIXED</td>
<td>0.166 (17%)</td>
<td>0.813 (12%)</td>
<td>0.813 (12%)</td>
</tr>
<tr>
<td>Chv</td>
<td></td>
<td>0.013 (15%)</td>
<td>-1.28 (215)</td>
<td>0.241 (199)</td>
<td>-</td>
</tr>
<tr>
<td>CLFO</td>
<td></td>
<td>5.0 (125)</td>
<td>20.3 (25.7)</td>
<td>0.471 (727)</td>
<td>0.471 (727)</td>
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<tr>
<td>Fat for volume</td>
<td></td>
<td>0.458 (27)</td>
<td>0.253 (772)</td>
<td>0.835 (12)</td>
<td>0.835 (12)</td>
</tr>
<tr>
<td>Proportional error</td>
<td></td>
<td>0.047 (20)</td>
<td>0.035 (55)</td>
<td>0.458 (12)</td>
<td>0.458 (12)</td>
</tr>
</tbody>
</table>

References

[5] Nomencl...