RESULTS

• In the subsequent backward elimination analyses, the effects of body weight on clearance and volume, and duration of treatment on clearance remained significant (Table 2).

Table 2. Summary of backward elimination results

<table>
<thead>
<tr>
<th>Model Parameter</th>
<th>Type of Reduction</th>
<th>SD Mean (95% CI)</th>
<th>SD Mean (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight</td>
<td>0.37</td>
<td>0.37</td>
<td>0.37</td>
</tr>
<tr>
<td>Time on Therapy</td>
<td>0.44</td>
<td>0.44</td>
<td>0.44</td>
</tr>
<tr>
<td>V</td>
<td>0.36</td>
<td>0.36</td>
<td>0.36</td>
</tr>
<tr>
<td>CL</td>
<td>0.50</td>
<td>0.50</td>
<td>0.50</td>
</tr>
</tbody>
</table>

• In total, 10 replicate data sets were simulated using the selected level of IOV (IIV/IOV=1.2) in drug variability (noise) when IOV is explicitly incorporated in the model.

• To model time-dependent PK, we can either find time-varying covariates that explain the variation in PK and incorporate the time-varying covariates in the fixed effect model or use IOV as a “fudge factor” to account for the variation in PK by explicitly modeling (in the random effect model). The concern is whether the model would still be able to discern the variation caused by time-varying covariates from natural deviations on measurement times.

• Incorporation of IOV generally warrants better estimation of parameters in the cases studied here.

CONCLUSIONS

• In this study, modafinil, a drug which exhibits enzyme auto-induction, for which duration of treatment is important, was selected for the simulation (see equations 2 – 6) and two different random effects model, including IOV or not including IOV (see equations 7 – 10). For the model not including IOV, was removed from equation 8. Covariate Analysis

• To model time-dependent PK, we can either find time-varying covariates that explain the variation in PK and incorporate the time-varying covariates in the fixed effect model or use IOV as a “fudge factor” to account for the variation in PK by explicitly modeling (in the random effect model). The concern is whether the model would still be able to discern the variation caused by time-varying covariates from natural deviations on measurement times.

REFERENCES


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