Bioequivalence of desmopressin in children

Introduction
Desmopressin (DDAVP) is a synthetic vasopressin analogue used in nocturnal enuresis treatment. Two formulations, a tablet (TAB) and a lyophilisate (MELT), exist of which the bio-equivalence has been established in adults but not in children. This study analyzes two clinical trials to investigate how the drug product and intake of food influence DDAVP pharmacokinetics in children and provides suggestions for subsequent studies.

Results
Three covariates were identified: body weight (on $V_d$), formulation (on $F_1$) and study effect (also on $F_1$). As the only difference between the studies was the administration of food, the study effect was assumed to be an indicator of the food effect. This food effect was demonstrated in adults ([4]) and is thus expected to be present in children as well. The parameter values, along with the estimated bootstrap values (198/1000 runs successful) are presented in table 1.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>SE</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\theta_1$</td>
<td>$\text{Fe}d$</td>
<td>$0.340$</td>
<td>$0.051$</td>
</tr>
<tr>
<td>$\theta_2$</td>
<td>$\text{F}ast$</td>
<td>$0.280$</td>
<td>$0.064$</td>
</tr>
<tr>
<td>$\theta_3$</td>
<td>$\text{F}ast$</td>
<td>$0.280$</td>
<td>$0.064$</td>
</tr>
</tbody>
</table>

Table 1: Population pharmacokinetic model parameter estimates and bootstrap values

To increase confidence in the model, the distribution of the normalized prediction distribution errors (NPDE) was examined, as shown in figure 1. Non-normality could not be detected using the Shapiro-Wilk test and the model was thus found to describe the data well.

Sensitivity Analysis
Being confident in the model, a sensitivity analysis was performed to determine optimal sampling points. As is depicted in figure 2, where the elasticity indices are plotted, the plasma concentrations are most sensitive to the model parameters in the early post-dosing phase. It is thus recommended to sample frequently in the time between 15 minutes and 2 hours post-dose. The period after six hours is also interesting to sample as the plasma concentrations are only sensitive to the clearance parameter then.

Bioequivalence and food effect
Four scenarios (Fed, Fasted, MELT and TAB) were simulated using the 50 patients (figure 3, 10 simulations per patient per scenario). The 90% CI for the geometric mean of the ratio of $AUC$ and $C_{\text{max}}$ were calculated and are presented below.

Conclusions
For the first time in children, the food effect on DDAVP pharmacokinetics was proven to be significant. 120pg MELT and 200pg TAB don’t seem to be bioequivalent. For further studies, sampling times should be suggested, which should result in more informative data.

References

Acknowledgments
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