Objectives

The primary objective of this analysis was to ascertain, through an integrated PK/PD model-based approach, what measures of change in heart rate (HR) should be considered as clinically relevant in phase I trials. Interindividual and between-study variability of the circadian variations of HR demand a more sophisticated approach than simple baseline-correction, when attempting to distinguish drug effects from usual changes in HR.

Methods

Placebo and predose hourly average HR data from 24-h holter monitoring from seven phase I clinical studies were pooled (n=405, >700 hr of daily recordings). The basic mathematical model consisted of a sum of five cosine functions to replicate the circadian variations in (with periods $p_1$ of 24, 12, 8, 6, 4.8 hours, respectively).

\[ H = H_{\text{mesor}} + \sum_{j=1}^{5} a_j \cos \left( \frac{2\pi}{p_j} (t - r_j) \right) \]

where $H$ denotes HR, $H_{\text{mesor}}$ the mesor or mean HR, $a_j$ the amplitude, $r_j$ the period and $t_j$ the phase shift of the $j$th cosine function.

Interindividual variability (IV) was assessed for $H_{\text{mesor}}$ and $a_j$ using a log-normal distribution. An example is given for the notional structural model parameter $P$:

\[ P = TVP \exp(\theta_P) \]

whereas IV for the phase shift $r_j$ was found to be normally distributed

\[ r_j = TVP + \eta_j \]

Residual variability was tested as additive or proportional or both.

Study, sex, and weight were tested during the covariate building of a non-linear mixed-effects model as well as the placebo effect compared to predose. Covariates were modeled similarly as the IV with $\exp(\theta_P)$ for $H_{\text{mesor}}$ and additive $+ \theta_P$ for $r_j$.

Covariates were first investigated for only the predose data and later for changes between predose and placebo during the treatment period.

Statistical shrinkage in empirical Bayes estimates (EBEs) of model parameters used for diagnostic purposes was evaluated as

\[ s_{P_k} = 1 - SD(\text{res})/SD(\text{tot}) \]

where $s_{P_k}$ is shrinkage in model parameter $P$, $SD(\text{res})$ is the standard deviation of the individual EBEs of IV in parameter $P$, and $\omega_P$ is the model estimate of the standard deviation in the IV associated with parameter $P$.

Results

Due to the high number of possible covariates (7 studies + 2 genders + weight)\(11\) parameters we applied several independent methods to find the optimal covariate model for the predose HR data. Monolix3.1\(1\) was able to run a full covariate model and did not find a significant effect of weight (results see Table 1). Xpose4\(2\) was used to fit a generalized additive model (GAM), which suggested very similar covariates as found with the Monolix full covariate model. Nonmem\(6\) showed large difficulties fitting the model such that a stepwise covariate search was not possible with the full data set (analysis of a subset of data large model such that a stepwise covariate search was not possible due to software memory capacities of Monolix3.1, therefore no standard errors or log-likelihood estimates could be derived for the full model).

Typical HR changes over the day were significantly different between studies (see Figure 3). HR over the day ranged from approximately 60 to 80 bpm (in a typical male subject). Gender differences could be found for the mesor (\(+0.6% \text{ or } +100\) bpm higher for a female subject), but no statistically significant study dependence was noted even though the covariates for the studies implied differences of 1.5-3.2 bpm. The placebo effect on the mesor was always smaller than this gender difference (0.5-6.3% increase).

Conclusions

\[ \text{Overall gender- and study-dependent effects were shown to influence the circadian changes of HR of the typical subject to a greater extent than what is considered to be a clinically relevant drug effect. However, not all the effects found to be statistically significantly different during model building could also be considered clinically relevant, especially a number of study-dependent effects on the amplitude parameters.} \]

\[ \text{Due to the high variability of HR over the day and the large study and gender dependencies, it is recommended to consider a model-based approach when estimating any potential drug effect compared to baseline and placebo during clinical trials.} \]

\[ \text{The hourly average used to collate the HR data provided a good estimator of the daily changes in HR, but is unable to describe short-term changes. Depending on the modeling objective, a finer level of granularity of the data (and thus a higher complexity of the model) might be more appropriate.} \]

Acknowledgements

We want to thank Niclas Jonsson for his work on a similar project that inspired this work.

References