Facilitating Cardiovascular Safety Exposure-Response Modeling in Early-Phase Clinical Studies with the cardioModel Package for R

Daniela J Conrado[1,*], Gregory J Hather, Danny Chen[1], William S Denney[1]

[1]Clinical Pharmacology, Pfizer Inc., Cambridge, MA; [*]Current address: Metrum Research Group, Wellesley, MA, danielac@metrumrg.com

Significance and Objectives

- Exposure-response (ER) analysis of QT interval in single ascending dose (SAD) and/or multiple ascending dose (MAD) phase 1 studies has been recently proposed as an alternative to the thorough QT study [1].
- A variety of ER models have been published describing drug effect on QT interval and other markers of cardiovascular (CV) safety.
- Therefore, we created the cardioModel R package to automatically evaluate models for assessing phase 1 CV safety data and identify the best fitting ER model.
- cardioModel can be used to describe the relationship between drug concentration and QT interval, blood pressure (BP), heart rate (HR) or pulse rate (PR).

Methods

- The selection of baseline and drug effect model structures included in the R package cardioModel was based on single- or multi-study ER or pharmacokinetic-pharmacodynamic (PK-PD) analyses on QT interval, BP, HR or PR published in the scientific literature before August 2013 (searching Pubmed, OVID MEDLINE, and Embase).
- An unstructured baseline model (i.e., estimation of a baseline value at each study nominal time after the first drug dosing, NTAFD) was also included based on our previous work [2].

Baseline models

$$Baseline = E_0$$

$$Baseline(t) = \sum_t E_{0,t(NTAFD=t)}$$

$$Baseline(T) = Mean + Amplitude \cdot Cosine\left(\frac{2 \cdot \pi \cdot T}{12} - Shift\right)$$

$$Baseline(T) = Mean + Amplitude \cdot Cosine\left(\frac{2 \cdot \pi \cdot T}{24} - Shift\right)$$

$$Baseline(T) = Mean + Amplitude_1 \cdot Cosine\left(\frac{2 \cdot \pi \cdot T}{12} - Shift_1\right) + Amplitude_2 \cdot Cosine\left(\frac{2 \cdot \pi \cdot T}{24} - Shift_2\right)$$

Drug effect models

$$Effect = Baseline + Slope \cdot Concentration$$

$$Effect = Baseline + \frac{E_{max} \cdot Concentration}{EC_{50} + Concentration}$$

$$Effect = Baseline + \frac{E_{max} \cdot Concentration^{\gamma}}{EC_{50}^{\gamma} + Concentration^{\gamma}}$$

t: nominal time after the first drug dosing. T: clock time.

Results

By considering multiple combinations of baseline and drug effect models, as well as multiple ways to set random effects, cardioModel includes 100 mixed-effects model structures.

Usage:

```
cardioModel(x, ID = "ID", NTAFD = "NTAFD", TOD = "TOD",
   RESPONSE = "RESPONSE", EXPOSURE = "EXPOSURE",
   PERIOD = "PERIOD", SEQUENCE = "SEQUENCE",
   COHORT = "COHORT", AIC.k = 2, study.name =
   "unknown study", drug.name = "unknown drug")
```

Arguments:

- x: A data frame with one measure of CV response (e.g., QT interval), and one measure of drug exposure (e.g., plasma concentration). This data frame contains the following columns:
  - ID: The subject identification number.
  - NTAFD: The nominal time after first dose.
  - TOD: The time of the day, as a continuous variable [0, 24).
  - RESPONSE: A measure of CV response (e.g., QT interval).
  - EXPOSURE: A measure of drug exposure (e.g., plasma concentration).
  - PERIOD (optional): The study period for studies where the subjects receive different doses at different occasions. If a column with this name does not exist, then it is assumed that there is only a single occasion. In this case, only models without between occasion variability will be fit.
  - SEQUENCE (optional): The sequence when multiple measurements of the response are taken with the same recorded value of NTAFD. If a column with this name does not exist, then it is assumed that multiple measurements are not recorded for the same subject at the same time.
  - COHORT (optional): The study cohort when period numbers are nested within cohorts. If a column with this name does not exist, then it is assumed that the period numbers are not nested within cohorts.
- AIC.k: numeric, the penalty per parameter to be used for computing the AIC; the default here is 2, which is the classical AIC.
- study.name (optional): The study name (for output labeling).
- drug.name (optional): The drug name (for output labeling).

Results

Output:

The output of cardioModel() is a data frame with a row for each of the tested models, ordered by ascending values of the Akaike Information Criterion. This data frame contains the following columns:

- MODEL: A brief description of the model formula.
- AIC: Akaike's Information Criterion for the fit.
- The next 11 columns ("SLOPE", "VAR.SLOPE", "EMAX", "VAR.EMAX", "EC50", "VAR.EC50", "COV.EMAX.EC50", "HILL", "VAR.HILL", "COV.EMAX.HILL", "COV.EC50.HILL") contain the parameter estimates and associated uncertainties.
- DRUG.EFFECT.DELAY: A diagnosis for anti-clockwise hysteresis which is performed to evaluate the appropriateness of the direct-link exposure-response analysis. The first derivative of the individual drug concentration is numerically calculated with respect to time. The derivative (x-axis) is plotted versus standardized (Pearson) residuals from the nlme (y-axis). A linear regression analysis is performed and the 99 percent lower confidence bound for the slope is calculated. If the lower confidence bound for the slope is greater than zero, then the presence of a drug effect delay is inferred, and the value will be "yes"; otherwise, the value will be "no".
- ERROR.MESSAGE: The error (if any) that occurred while fitting the model.

Conclusions

- The cardioModel suite of models provide a unique opportunity to estimate and predict drug effects on CV safety markers for a small phase 1 study in a standardized and simplified manner.
- The cardioModel package will be made available to the public via the Comprehensive R Archive Network (CRAN).

References

[1] Darpo B et al. Clin Pharmacol Ther 2015; 97:326-35.
[2] Conrado DJ, Chen D, Denney WS. Clin Pharmacol Ther 2014; 95: S18-19.

Acknowledgments

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**This poster is based on version 0.3 of cardioModel.