Safety pharmacology screening using a standardized population pharmacokinetic-pharmacodynamic modelling approach.

N. Snelder[1], T. van Steeg[1], B. Ploeger[1], N. Atkins[2], P. van der Graaf[2]

1. LAP&P consultants, Leiden, The Netherlands
2. Pfizer Global Research & Development, Sandwich. Kent. CT13 9NJ, UK.

Contact: n.snelder@lapp.nl

Leiden Experts on Advanced Pharmacokinetics & Pharmacodynamics

Background

- Translational PKPD modelling has been recognized as an efficient tool for bringing forward early insights in drug efficacy and safety into the clinical development stage.
- Detailed understanding of the safety pharmacology of NCE's early in development is essential for the prediction of potential safety issues in the clinic.
- At Pfizer, the safety pharmacology of lead compounds is routinely investigated in rats using a standardized study design, resulting in a high volume (up to several studies per week) of studies that require rapid PKPD analysis. To obtain information on day-night differences and handling effects a vehicle group is included in the study design.
- A standardised PKPD modelling approach is suggested in order to efficiently use the information from the standard safety studies.

Objectives

Main objective

- Timely go-no go decisions in NCE safety issues

Secondary objectives

- Determination of concentration resulting in a pre-defined effect level
- Quick turnaround from data to results (<2 days)
- Development of a Standardised Modelling Approach (SMA) which allows PKPD assessment by less-experienced modellers

Methods

Study design

- Oral administration of NCE for PKPD characterisation
- PK characterised in small satellite group (typically 4 rats, 6 samples in 24h)
- PD obtained in telemetry implemented rats (vehicle and 1-3 dose levels, 8 rats per group). Heart rate and blood pressure recorded 1h predose up to 24h postdose

Methods cont.

Software

- An S-plus script (S-PLUS® 8.0) was used to generate the dataset. A standardised xls-file was used as input.
- NONMEM v.6.2 with an in-house available NONMEM-S-PLUS interface was used for modelling

SMA

PK Modelling

- 8 standard models for structural PK model development.
  - One- and two compartment models
  - 1st and 0-order absorption models
  - Evaluation of saturable clearance/absorption
- Evaluation of stochastical model (IIV and error model)

Criteria

- MVOF compared to parent model and a drop of 3.84 points ($p<0.05$) is considered a significant improvement
- Final model minimization and COV step successful

SMA cont.

PD Modelling

1st *Development baseline & placebo model*

- Evaluation of day-night difference and handling effect

2nd *Development drug effect model*

- Use final baseline model
- Graphical evaluation of hysteresis/proteresis (clear hysteresis → use effect compartment model in next step)
- Evaluation of drug effect using the following structural models: linear model, power model, (sigmoid) E_{max} model, Hockey stick model and a log-linear model
- Evaluation of IIV (maximum 2 random effects and exponential only) and error model

Criteria

- In case of proteresis → model transferred to experienced modeller
- MVOF compared to parent model and a drop of 10.8 points ($p<0.001$) is considered a significant improvement (parent model is defined in SMA)
- Final model minimization and COV step successful

Results

• The standardised PKPD modelling approach provided detailed guidance on the modelling process, i.e. which models should be evaluated and how to interpret the modelling results. The SMA allowed a less-experienced modeller to asses the PKPD for multiple compounds without assistance.

• The PKPD relationship was characterised by three modellers with different modelling experience within the required timelines (2 day turnover) for six compounds. The obtained results (final models for PK and PD) were identical.

• The standard output for HR and BP could be summarized in two figures (PKPD relationship for BP & HR, i.e. figure 1-4) and two tables (table 1 & 2)

Heart Rate

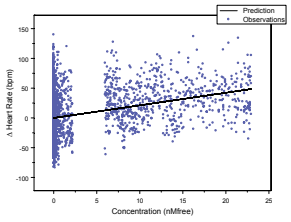

Figure 1, example of a linear drug effect model identified for Heart Rate

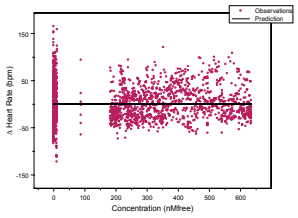

Figure 2, example of no drug effect identified for Heart Rate

Blood pressure

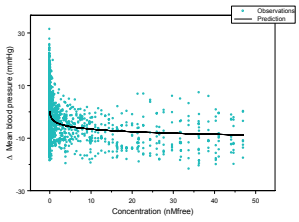

Figure 3, example of a log-linear model identified for Blood pressure

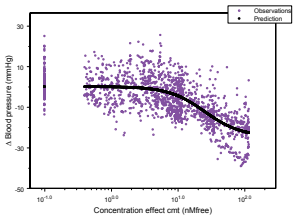

Figure 4, example of a sigmoid E_{max} model identified for Blood pressure

Tables

Table 1, Example table for concentration resulting in a pre-defined effect level (heart rate)

Δ HR (bpm)	Concentration (ng/mL)	Concentration (nM free)
+25	24.6	2.40
+50	60.7	5.92

Table 2, Example table for concentration resulting in a pre-defined effect level (blood pressure)

Δ MBP (mmHg)	Concentration (ng/mL)	Concentration (nM free)
-5	32.8	3.20
-10	1143	111.5

Hysteresis/Proteresis

- During the validation it was observed that figure 5 is essential to guide the less-experienced modeller with regard to the presence of hysteresis or proteresis in the concentration-effect relationship.

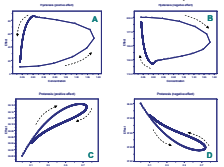

Figure 5, Assesment of hysteresis and proteresis for less-experienced modeller

Conclusion & Perspectives

- The developed standardized PKPD modelling approach for safety pharmacology screening allows quick (2 day turnover) and easy identification of the concentration- (side) effect relationships of discovery compounds in a routine based setting.
- We are currently in the process of implementing this approach into a desktop tool which will perform most of the analysis in a semi-automated manner.
- Currently, this approach has been validated to describe data from one type of rat study. However, it is foreseen that this standardized approach can be applied to other study designs also. Such a standardised approach towards PKPD analysis may also have applications outside safety testing.

References

[1] Danhof, M., de Lange, E.C., Della Pasqua, O.E., Ploeger, B.A. and Voskuyl, R.A.: Trends Pharmacol Sci, 29: 186-91. Epub 2008 Mar 18. (2008)