PK/PD modelling: a useful tool to train people to better design *in vivo* chronic study in ob/ob mice

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Introduction

In preclinical research, the results from early pharmacokinetic/pharmacodynamic (PK/PD) studies are very often not enough discussed between pharmacologists and modellers before the design of the pivotal *in vivo* study and sometimes fail to generate relevant data.

The interest of assessing PK in the same studies as PD in order to characterize the PK/PD relationship is rarely taken into account by project management.

Objectives

This work is to illustrate how PK/PD M&S can assist the study design, and lead to the generation of quality data. Ultimately, we aim to make the pharmacologists, *in vivo* techniciens and project leader in research and development sensitive to PK/PD modelling.

Methods

Part I: before the 28 days PK/PD study:

- *Available study/data:*
  - Single oral administration PK study at dose 2 => plasma concentrations
  - 3 days PD study => blood glucose level (BGL) and insulin concentration after (oral glucose tolerance test) OGTT on day 3 (2 groups: placebo and drug S at dose 4)
- *Early modelling using a naive-pooled approach within Phoenix® [1]:*
  - PK model building and simulation of plasma concentrations after repeated administration at dose 4
  - PK/PD model building:
    - ➢ Placebo model and effect of S drug on BGL using the plasma concentrations simulated using the PK model
- *Optimal design [2]:* using PopED lite and the PK model to optimize the PK sampling times for the 28 days PK/PD study

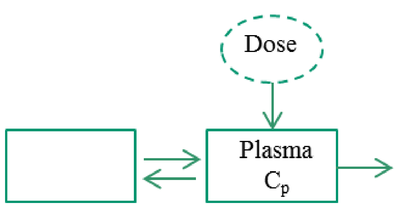
Part II: after the 28 days PK/PD study:

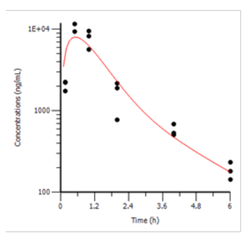
- *Available data:*
  - Plasma concentrations of S drug after repeated oral administrations at dose 1, dose 2, dose 3 and dose 4 on day 13
  - Basal BGL on day 0, day 7, day 14 and day 28, under placebo and treatment
  - BGL and insulin concentrations of day 21 after OGTT, under placebo and treatment
  - HbA1c on day 0 and day 28, under placebo and treatment
- *Modelling using a population PK/PD approach within NONMEM [3]:*
  - PK model building using all the concentrations on day 13 and the plasma concentrations after a single oral administration at dose 2
  - PK/PD model building:
    - ➢ Placebo model for BGL, insulin and HbA1c
    - ➢ Effect of S drug on BGL and HbA1c (on going)

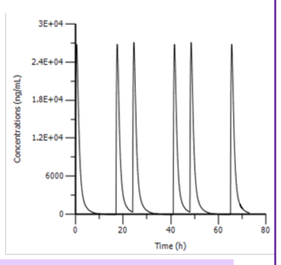
Results

Part I: before the 28 days PK/PD study:

- **PK model:**

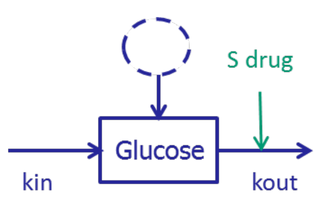


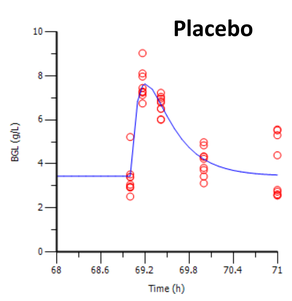


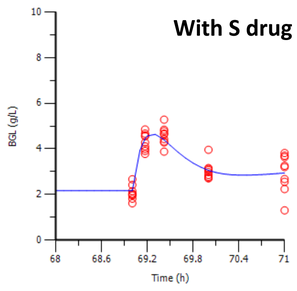


Assumptions:
⇒ Linearity of the PK between doses (dose 2 and dose 4)
⇒ Linearity of the PK between days (day 1 and day 3)
⇒ PK fixed for the PK/PD model

- **PK/PD model:**





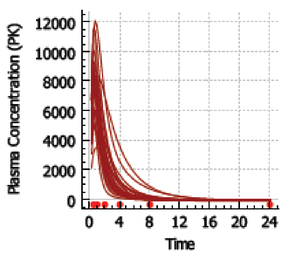


⇒ low precision of estimation for some parameters
⇒ PK fixed to population values, so all the variability was on PD

This preliminary modelling was very helpful in convincing project stakeholders of the interest of the approach

Optimal design for PK samples :

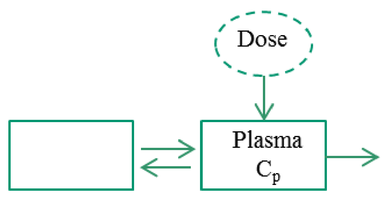
- **PK model:** 2-compartment model with first order oral administration

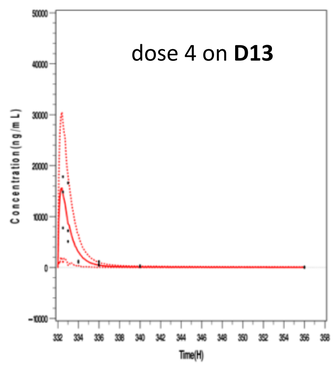


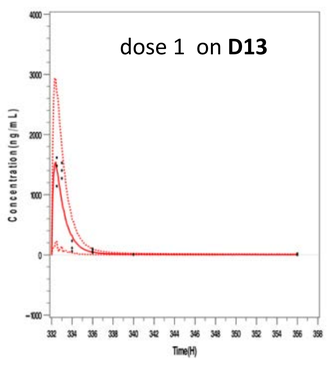
- Optimized design: 0.2, 1.8, 3.2, 5.2, 11.8 and 23.6 h
- Discussion with the pharmacologists concerning the study feasibility
  - ⇒ samples for PK in the 28 days PK/PD study on D13
  - ⇒ samples matrix with 0.5, 1, 2, 4, 8 and 24 h

Part II: after the 28 days PK/PD study

- **PK model:** 2-compartment model with first order oral administration induction on CL between day 1 and day 13

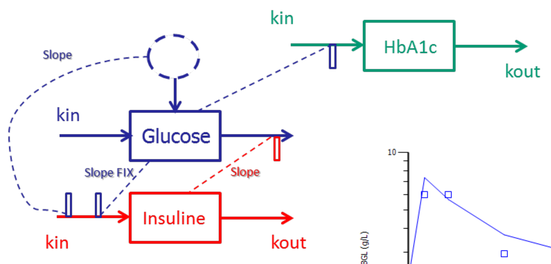




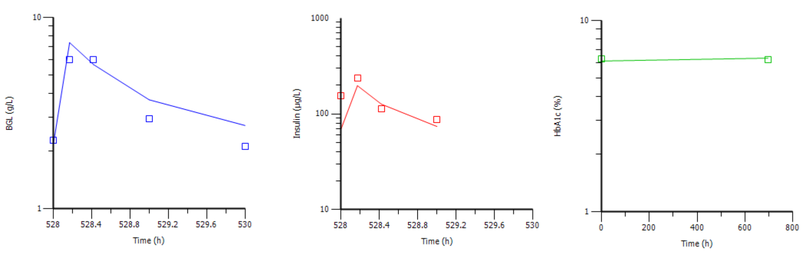


- Inter-individual variability on clearance and peripheral volume
- Induction on clearance => non linearity on PK between D1 and D13

- **PK/PD model:**



ob/ob mouse n° 2 – placebo group



- Inter-individual variability on basal BGL, basal insulin and basal HbA1c
- In placebo group BGL often > ULOQ => taken into account by modelling
- Effect of S drug on going

Conclusions

Early discussions between pharmacologists and modellers in the preclinical development help to better design PK/PD studies in order to well characterize the PK/PD relationship. To be part of the drug development at the beginning allows to propose a modelling strategy for the translational drug development from animal to human.

Perspectives:

- Reference compound was also used as a comparator in the 28 days PK/PD study, which will be used as a proof of concept for the transposition into man
- The same 28 days PK/PD study will be performed in high fat diet mice. PK/PD model will be enriched with these data in order to define the best *in vivo* model to predict the effect on a new compound in type 2 diabetes patients.
- The addition of data generated in other animal models will allow for a robust translational approach.

References:
[1] Phoenix, WinNonlin 6.3 (Pharsight)
[2] PopED lite (University of Uppsala, Sweden)
[3] NONMEM 7.3