Multi-species translational PK/PD modelling in type 2 diabetes

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Context

In type 2 diabetes (T2D), several animal models are routinely used by the pharmacologists. Being able to describe the outcome of pharmacology studies (*e.g.* glucose tolerance tests, basal glucose and insulin), a single mechanistic PK/PD framework is of high value for compounds screening, support to dose selection in animals, and translation of the outcomes in patients.

In this context, a PK/PD model was developed in ob/ob mice for a S Drug and a reference compound (Rosiglitazone). However, the disease features are different in each species and have to be well characterised using data without treatment before any compound effect transposition.

Objectives

- To scale S drug PK/PD model in monkeys to support dose-efficacy assessment
- To refine the T2D disease model through PK/PD scaling in patients using literature data

Methods

1) Building the PK/PD model in mice:

- PK models for S Drug and Rosiglitazone
- PK/PD model w/wo treatment

NONMEM version 7.3.0.

2) Support to study design in diabetic monkeys:

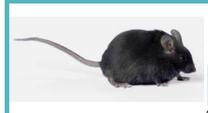
- Allometric scaling of the PK model for S Drug
- Transposition of the system related parameters using allometry

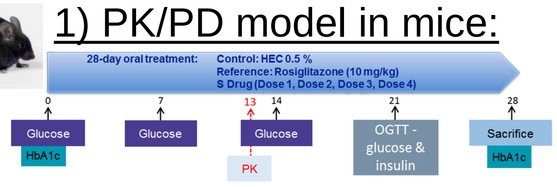
3) Disease model refinement through PK/PD scaling in T2D patients:

- Comparison with literature:
  - ✓ Disease model (wo treatment)
  - ✓ PK model for rosiglitazone
  - ✓ PK/PD scaling (with rosiglitazone)

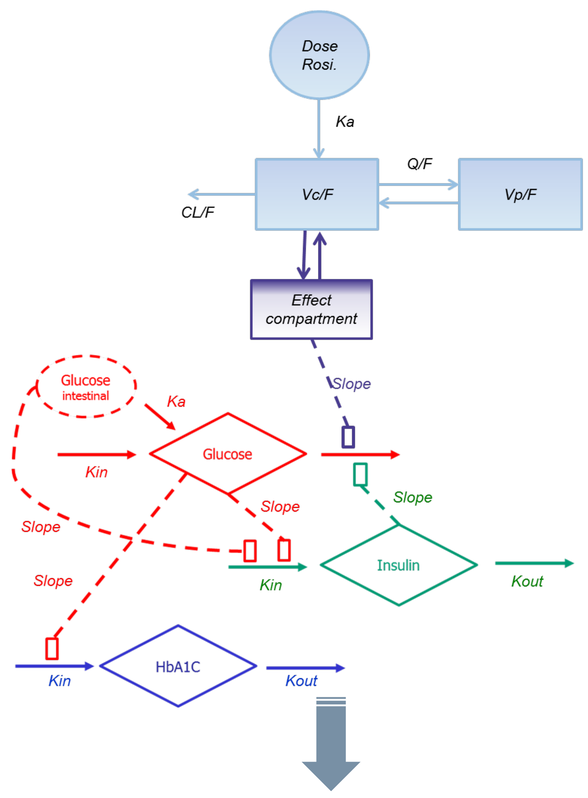
Results

1) PK/PD model in mice:





Design of the efficacy study

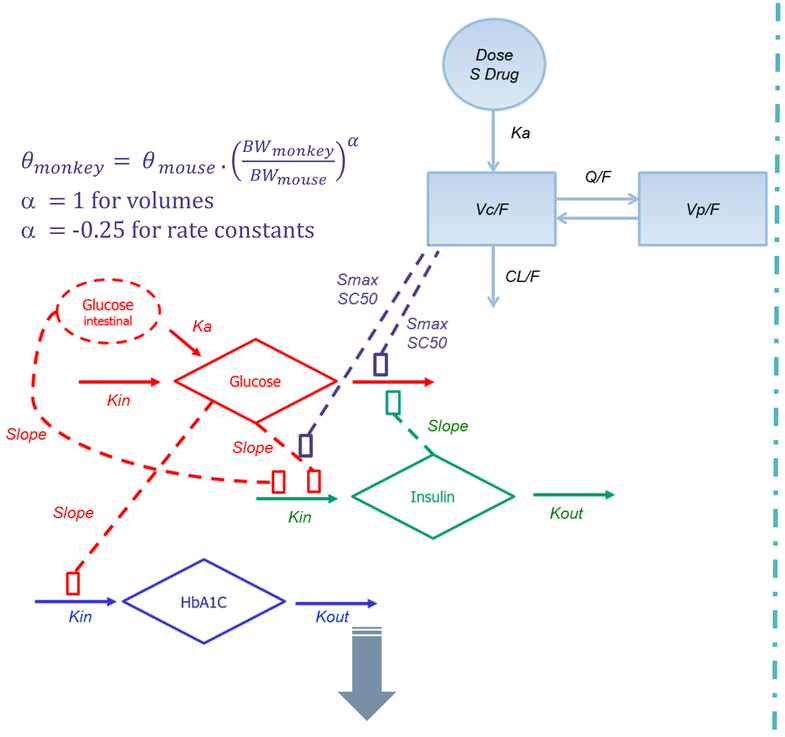


2) Prediction of an active dose in diabetic monkeys:

⇒ **Inter-species translation**
Scaling of system parameters

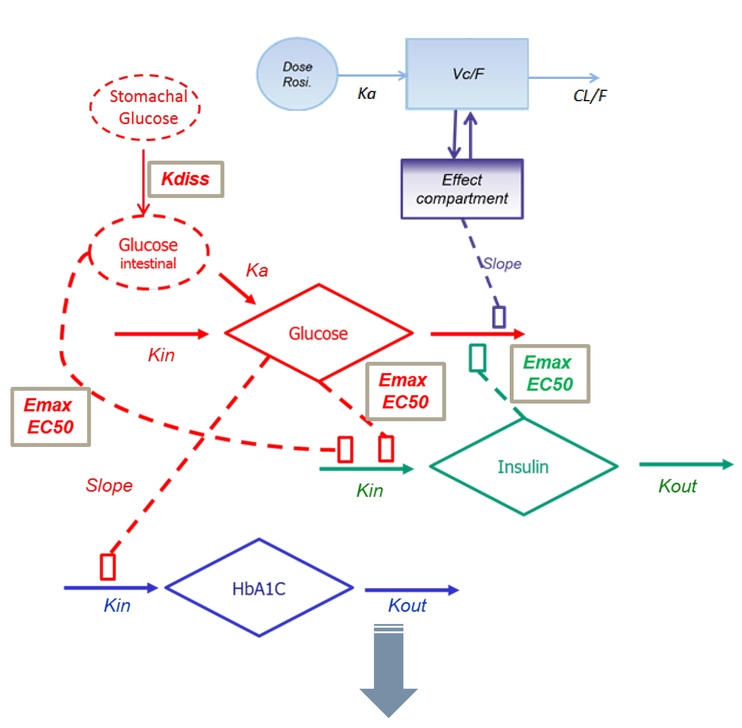
$$\theta_{monkey} = \theta_{mouse} \cdot \left(\frac{BW_{monkey}}{BW_{mouse}}\right)^{\alpha}$$

α = 1 for volumes
α = -0.25 for rate constants



3) Refinement of the disease model in patients:

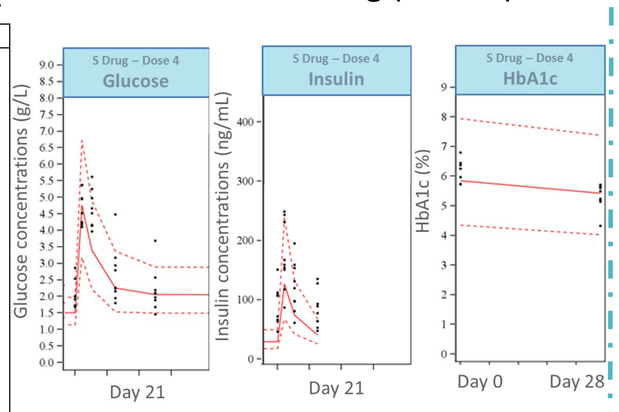
⇒ **Refinement of the disease model in patients**



Population PK/PD parameters in mice

Parameters (units)		VALUE	RSE (%)
KA_GLC	(h^{-1})	6.95	6.98
Kin_GLC	(g/h)	0.017	-
V4_GLC_INS	(L)	0.00904	-
ADD_GLC	(g/L)	0.536	2.85
Kout_INS	(h^{-1})	13.7	-
Kin_INS	(µg/h)	0.558	-
Slope_GLC	(L/g)	2.91	-
Slope_INS	(L/µg)	0.0199	-
ADD_INS	(µg/L)	28	3.55
Slope_gut_GLC	(g^{-1})	381	-
Kout_HBA1C	(h^{-1})	0.0012	-
Kin_HBA1C	(%/h)	0.0175	3.21
ADD_HbA1c	(%)	0.446	8.52
Slope_Glc_HbA1c	(L/g)	0.16	3.85
Slope_Rosi	(L/µg)	0.00113	-
keo_Rosi	(h^{-1})	0.00472	-
Smax_SDrug	(L/µg)	2.73	28.8
SC50_Sdrug	(µg/L)	633	42.7
Smax2_Sdrug	(L/µg)	0.264	241
SC502_Sdrug	(µg/L)	10	1690

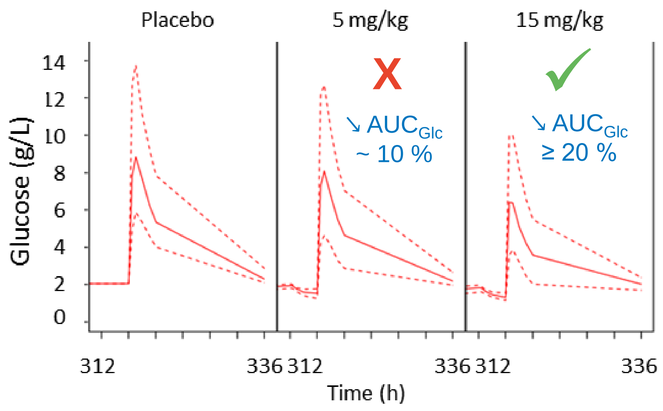
VPC after S Drug (Dose 4)



- Good description of the 3 biomarkers

— Median model-prediction
-- Inter-individual variability
• Observation

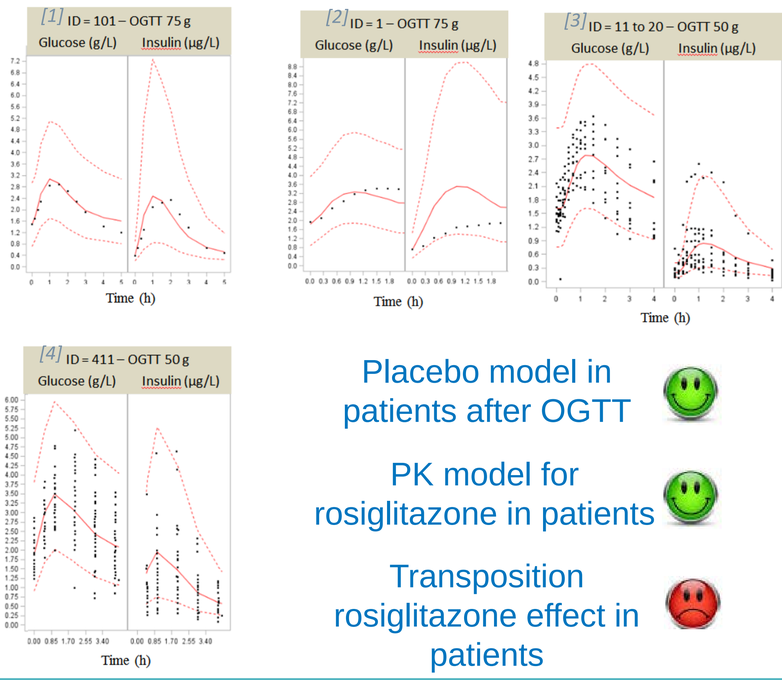
Glucose *versus* time during OGTT



- Prediction of an active dose in diabetic monkeys
- No *in vivo* results for this study

⇒ Need to refine placebo model in diabetic monkeys ?

VPC in placebo groups



Placebo model in patients after OGTT

PK model for rosiglitazone in patients

Transposition rosiglitazone effect in patients

Conclusion

In order to propose a relevant translational modelling strategy for drug development, the disease should be well understood and its specificities modelled in each species, as well as in patients. This scaling operations are far from being trivial and reference compounds are very useful in characterising the disease in each population.

MID3 value: medium impact as justification of doses selection.[5]

References:

1. Moller J. et al. Body composition is the main determinant for the difference in type 2 diabetes pathophysiology between Japanese and Caucasians. Diabetes care. (2014) 37 (3) : 796-804
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5. Workgroup EM, et al. Good Practices in Model-Informed Drug Discovery and Development: practice, Application, and Documentation. CPT (2016) 5 (3) : 93–122