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MODELLING THE WHOLE-BODY PHARMACOKINETICS (WBPK) OF RADIOLABELED GLYBURIDE IN HEALTHY VOLUNTEERS

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INTRODUCTION

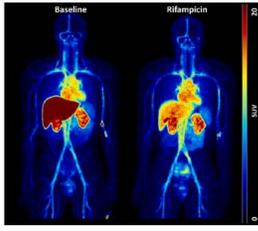


Fig 1: Whole-body PET imaging [2]

- Microdosing approaches:
 - administration of infra-therapeutic doses of drug candidates to volunteers
 - relatively facilitating regulatory framework
 - sometimes referred to as phase 0 [1]

PK studies using PET (positron emission tomography) imaging [Fig 1]: a quantitative, kinetic and ultrasensitive imaging technique

- A microdose PET study performed in healthy volunteers using the substrate Glyburide as a model drug[2]:
 - to assess the role of Organic Anion-Transporting Polypeptides (OATP) for liver uptake
 - their impact on whole-body pharmacokinetics (WBPK)

The **aim of this work** was to model the WBPK of radiolabeled glyburide (^{11}C -glyburide) with or without pre-infusion of rifampicin, a potent inhibitor of OATPs[2].

METHODS

DATA

- Two imaging sessions the same day [Fig2]: ^{11}C -glyburide with and without pre-infusion of 9 mg/kg of rifampicin

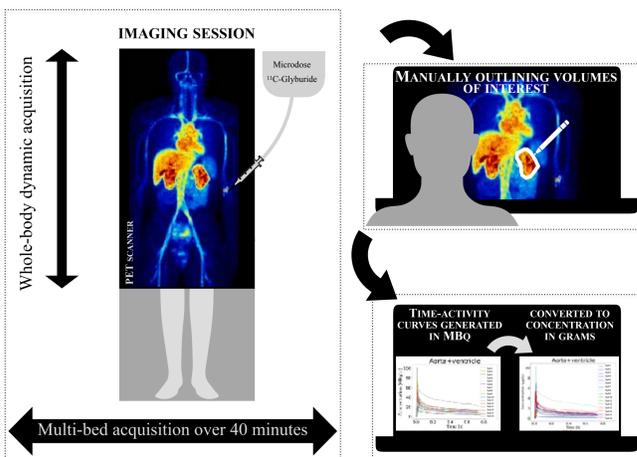


Fig 2: Data acquisition

- 16 subjects divided in group based on sex and age
- 5 organs used in the analysis: aorta+ventricle (blood), liver, kidneys, pancreas, spleen

NONLINEAR MIXED EFFECT MODELLING (NLMEM)

- Structural model construction using the 1st occasion:
 - Each organ using standard compartment models
 - Selecting for all 5 organs:
 - number of compartments for each organ
 - pancreas and spleen: a simple ratio of organ to blood concentrations was tested due to a rapid distribution
 - linear and non-linear rate constants for distribution and elimination
 - residual error model: proportional, constant or combined

- Statistical model construction using both occasions:
 - Interoccasion variability (IOV)
 - Body weight (allometric model on volumes of distribution)
 - Using the COSSAC algorithm[3]
 - Covariance structure simplified by removing variabilities if RSE > 100%
 - Assessment using graphical diagnostics (Visual Predictive Check (VPC))

- Model selection: Bayesian Information Criterion (BIC)

Monolix - 2023R1 was used for NLMEM.

RESULTS

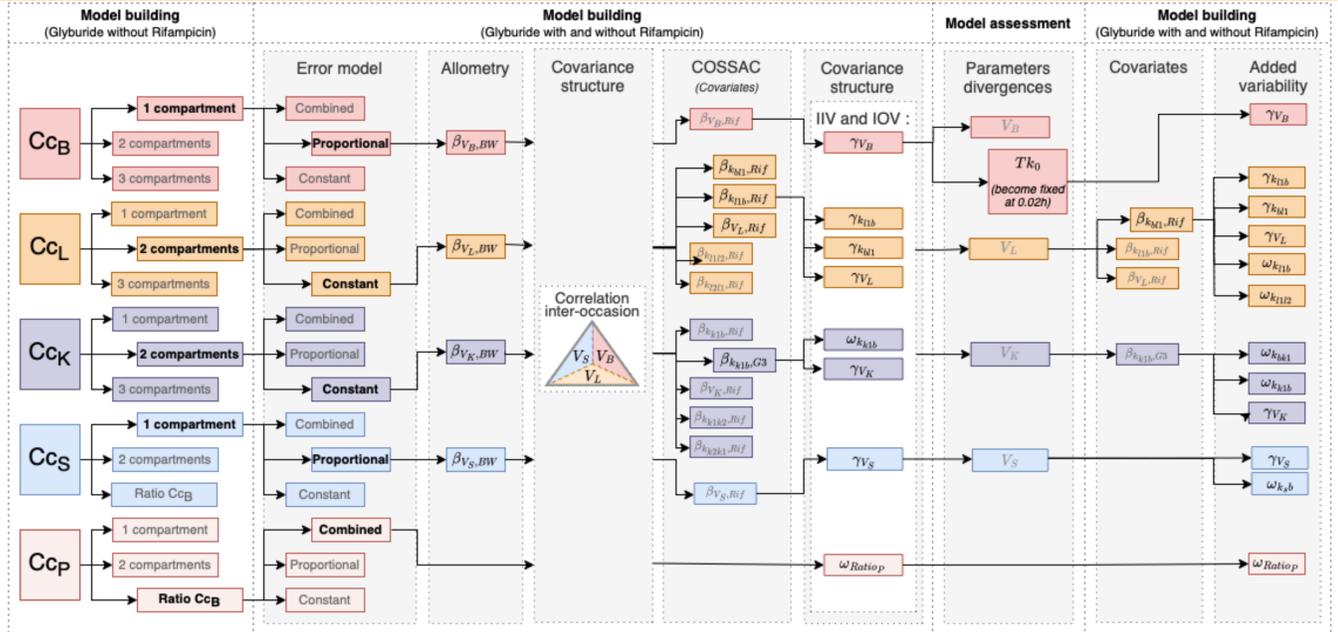


Fig 4: Model building process

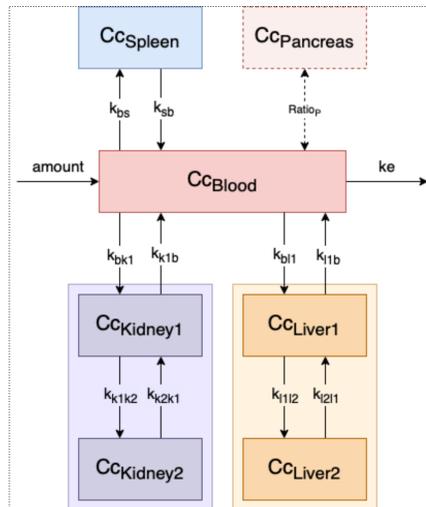


Fig 3: Structural model

- 6 compartments included in the final model [Fig 4]:
 - liver and kidney: two compartments each [Fig 3]
 - spleen: one compartment
 - pancreas: ratio with blood concentrations, rapid equilibrium both

- Adding covariates and correlation [Tab 1]:
 - body weight: allometric model on volumes
 - correlation between IOV random effects: V_{Blood} , V_{Liver} and V_{Spleen}
 - rifampicin decreased distribution blood to liver, transfer rate decreased by 32 %
- Visual predictive check [Fig 5]:
 - 1st occasion: good fits for the typical profiles in the different organs
 - 2nd occasion: model underprediction in blood, translating to a similar pattern in pancreas and spleen
 - VPC correct when fitting each arm separately

	Group 1 Men over 50 years old	Group 2 Women over 50 years old	Group 3 Men younger than 30 years old
Number of subjects First imaging session (Second imaging session)	4 (1)	5 (4)	7 (5)
Age (years) Median (Min - Max)	58.6 (50.2 - 63.5)	59.6 (58.8 - 64.6)	24.5 (20.3 - 30.3)
Body Weight (kg) Median (Min - Max)	81 (74 - 88)	66 (53 - 72)	73 (59 - 87)

Tab 1: Demographic characteristics of the 3 groups

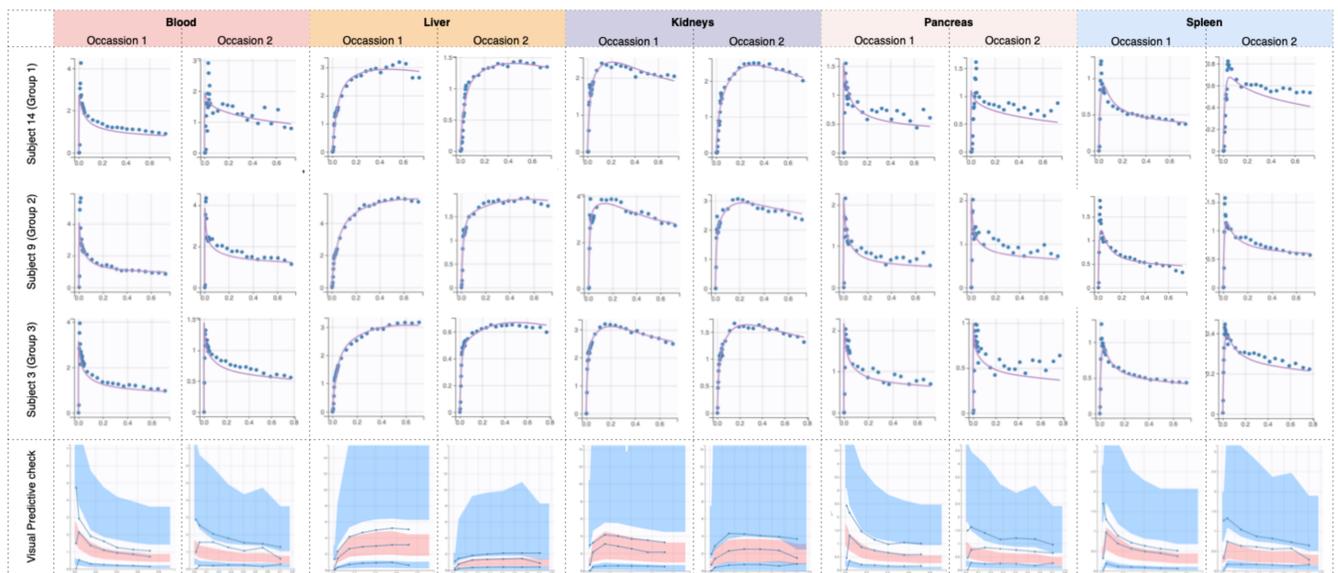


Fig 5: Individual fits and Visual Predictive Check

DISCUSSION

- WBPK of radiolabeled glyburide in 5 organs described using a compartmental model
 - liver distribution decreased in the presence of rifampicin, consistent with previous results from a non-compartmental analysis showing a reduced AUC [2]
- Comparison with a previous analysis using blood concentrations[4]
 - elimination rate (0.67 hr⁻¹) half of previous estimate
 - smaller central volume of distribution ($V_B = 0.45\text{L}$)
 - difficulties to estimate elimination reliably due to the limited observation period (40mn)

- Another issue: PET studies measure total radioactivity
 - blood sampling performed in the present study showed that less than 10% of the total dose was metabolized
- Rapid equilibrium between blood and pancreas (target tissue for antidiabetic effect)

PERSPECTIVE

- Combine PET data with preclinical PK studies using Bayesian approaches to predict the WBPK of investigational drugs even before traditional Phase I studies.

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