MECHANISTIC RESEARCH IN THE PREDICTION OF PHARMACOKINETIC PARAMETERS AND THEIR VARIABILITY IN CHILDREN: PROJECT PLAN.

H. T'jollyn[1], K. Boussery[1], K. Allegaert[2], J. Van Bocxlaer[1], G. Mannens[3], J. Snoeys[3] and A. Van Peer[4]

[1] Laboratory of Medical Biochemistry and Clinical Analysis, Faculty of Pharmaceutical Sciences, Ghent University, Harelbekestraat 72, B-9000 Ghent, Belgium

[2] Neonatal Intensive Care Unit, Division of Woman and Child, University Hospitals Leuven, Campus Gasthuisberg, Herestraat 49, B-3000 Leuven, Belgium

[3] Johnson & Johnson Pharmaceut Res & Dev, Div Janssen Pharmaceut NV, Preclin, B-2340 Beerse, Belgium

[4] Johnson & Johnson Pharmaceut Res & Dev, Div Janssen Pharmaceut NV, Clin Pharmacol, B-2340 Beerse, Belgium

1. Introduction

In drug discovery and development, pediatric research is hampered by ethical and economical considerations. If pharmacokinetic (PK) data in pediatrics are required, the first dosage is often assessed empirically. However, in the first two years of life important physiological changes cause major differences and a high variability in PK parameters when compared to adults (Figure 1). Specific argumentation concerning dosage adjustment for children is frequently missing because pharmacokinetic-mechanistic knowledge is inadequate[1,2].

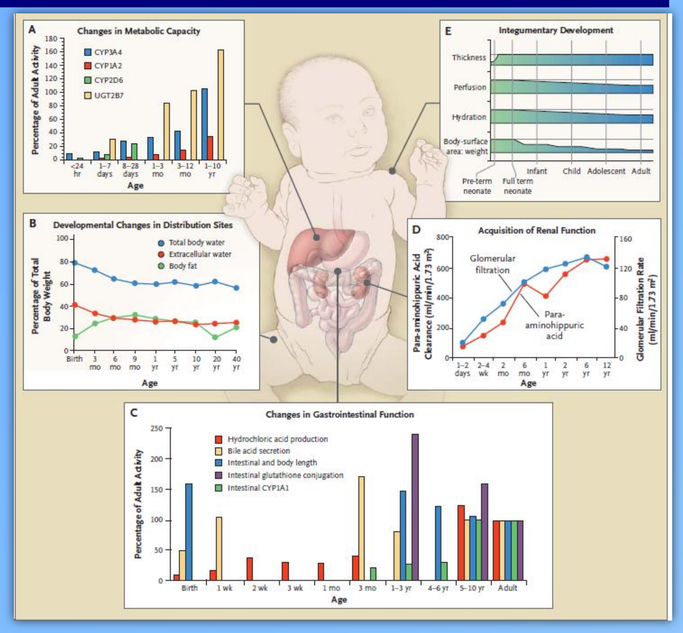

Figure 1: Developmental changes in physiologic factors that influence drug disposition in infants, children, and adolescents[2].

Drug exposure in children can be predicted using extrapolation techniques based on bodyweight and body surface area. However, much more complex models are needed that take into account all known biological factors and their variability to make reliable predictions, especially toward neonates and infants[3].

2. Simcyp®: a Physiologically Based PharmacoKinetic model

Physiologically Based PharmacoKinetic (PBPK) models are currently the ultimate tools to describe drug exposure in a physiologically realistic compartmental way. In this manner, the physiological changes occurring in childhood can be integrated to predict absorption, distribution, metabolism and excretion over the pediatric age range. Figure 2 represents the simplified algorithm structure of the Simcyp® PBPK model to predict drug elimination and distribution in pediatrics.

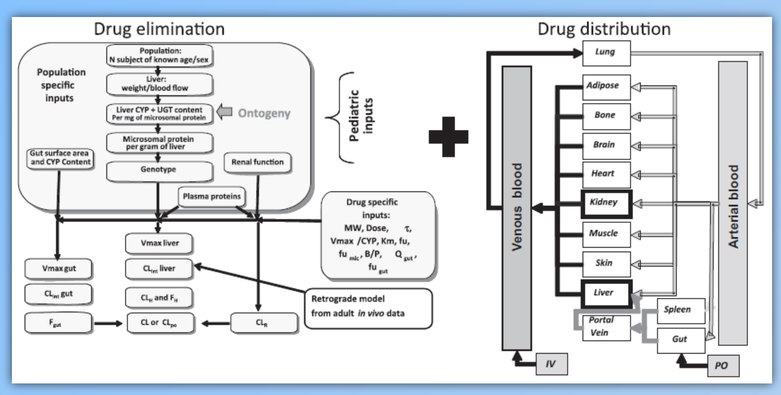

Figure 2: schematic representing the basic Simcyp® algorithms for the prediction of drug elimination and distribution in pediatrics[3].

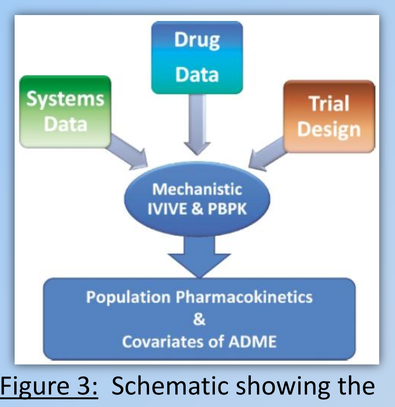

Figure 3: Schematic showing the principial elements of a population-based simulation platform[4].

Simcyp® is a population-based ADME simulator which means that it predicts ADME parameters based on a population approach. Three requirements for such models are needed (Figure 3). Systems data include physiology, biology, biochemistry; drug data include molecular weight, logP, pKa, CLint; trial design includes population size, administration route, dosage interval, etc.

3. Objectives

With an available *in vivo* pediatric PK data set of iv tramadol and propofol as a reference, this project consists of 3 sections:

1. Initial validation of the Simcyp® PBPK model in adults

   from *in vivo* and *in vitro* literature data ⟶ prediction of adult PK

2. Validation of the Simcyp® pediatric PBPK model

   (top-down) from *in vivo* adult PK data ⟶ prediction of pediatric PK

   (bottom-up) from *in vitro* data ⟶ prediction of pediatric PK

3. Identifying the differences between observed and predicted values and their variability

   in consultation with the Simcyp® PBPK model developers

   by conducting *in vitro* experiments

   ⟶ integration of missing mechanistic information into the model

4. Current Progress

The initial validation: TRAMADOL in adults

A. Volume of distribution (Vd)
   - reference= 210 L (3 L/kg)
   - predicted Vd:
     i. RR-model= 0.72 L/kg
     ii. RR+ Grunexp= 2.53 L/kg

B. Clearance (CL)
   - reference= 28 L/h
   - predicted CL= 14.16 L/h (accounts for CYP2D6, 3A4)

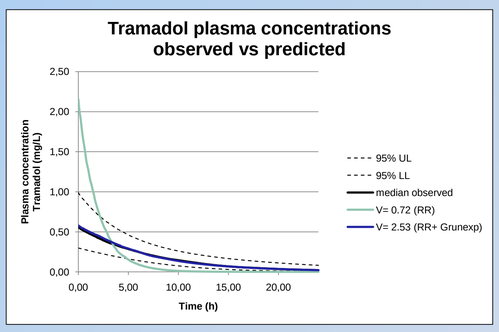

Figure 4: the observed vs predicted plasmaconcentration-time profiles for tramadol in the assesment of the Vd

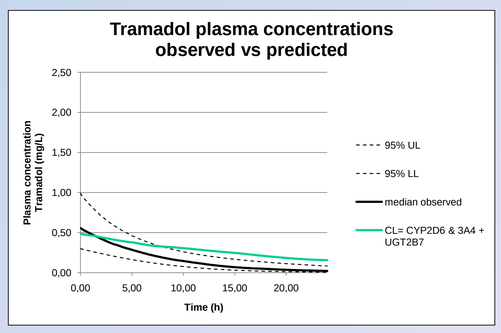

Figure 5: the observed vs predicted plasmaconcentration-time profiles for tramadol in the assesment of the CL

5. Conclusion and Future plans

Normally, when a parameter (Vd, CL) is estimated within the 2-fold value of the observed parameter, this is considered a good prediction. We conclude that volume of distribution (2.53 L/kg) is well predicted (using in part experimental values), but the prediction of clearance (14.16 L/kg), although situated in the 2-fold interval, still needs optimization.

In the future we wish to optimize the prediction of PK parameters and their variability toward children by identifying the mechanistic gaps in the PBPK model in order to improve the prediction of drug exposure in pediatric drug development.

6. References

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