Universiteit Leiden
The Netherlands

Impact of renal transporters on pediatric renal clearance using PBPK modelling

Sînziana Cristea[1], Elisa A.M. Calvier[1], Amin Rostami-Hodjegan[2,3], Elke H.J. Krekels[1], Catherijne A.J. Knibbe[1,4]

Cluster Systems Pharmacology

INTRODUCTION

Active transport can have an important impact on renal clearance (CL_R).

The influence of transporter maturation on CL_R in children has not been studied in detail.

Physiology-based models that incorporate maturation of active transporters are needed to predict realistic CL_R across the pediatric age-range.

Aim: To develop a PBPK function to study the impact of renal transporters and their maturation on CL_R for different pediatric age-ranges and drug properties.

METHODS (1)

For CL_R simulations, published PBPK functions (Equation 1)[1] and *in vitro-in vivo* (Equation 2)[2] extrapolations were used.

Maturation functions were included for plasma protein binding[3], kidney weight[4], renal blood flow[5], glomerular filtration rate[6] and transporters capacity[7].

Abundance and the number of proximal tubule cells were kept at adult values[8,9].

21600 hypothetical drugs were generated and their CL_R was simulated for 11 virtual individuals with realistic demographics[8] for ages between 1 day and 35 years.

CONCLUSION

We made the first pediatric PBPK function to assess the contribution of active tubular secretion to CL_R in children:

- The contribution of active tubular secretion is important and is dependent on transporter abundance and intrinsic clearance. Active transport is likely to be the primary elimination route for certain drugs.
- Quantifying maturation of transporter abundance and activity, could lead to improved predictions of CL_R in children.
- The function for extrapolation of CL_R from adults to children can improve dosing optimization in the pediatric population.

METHODS (2)

Drug Specific Parameters

- Fraction unbound ($f_{u\text{-}HSA}$)
- Blood-to-plasma partition coefficient (BP)
- Intrinsic Clearance ($CL_{int,T}$)
- Fraction Reabsorbed (f_{reab})

System Specific Parameters

- Kidney weight
- Renal blood flow (Q_R)
- Glomerular Filtration Rate (GFR)
- Maturation of Transporters Capacity (mat_{TC})
- Relative abundance factor (RAF)
- Proximal Tubule Cells (PTCPGK)

Equation 1

$$CL_{int,sec} = \sum_{j=1}^{N_{transporter}} mat_{TC} \times RAF_j \times CL_{int,T,j} \times PTCPGK \times Kidney\ weight$$

Equation 2

$$CL_R = Q_R \times \left(GFR \times \frac{f_{ub}}{Q_R} + \left(1 - \frac{GFR}{Q_R}\right) \times \frac{f_{ub} \times CL_{int,sec}}{Q_R + \frac{f_{ub} \times CL_{int,sec}}{BP}} \right) \times (1 - f_{reab})$$

RESULTS

- Impact of active transports on CL_R remains fairly constant for all ages (Figure 1) for different relative abundance factors (RAF) and intrinsic clearance ($CL_{int,T}$) values.
- For $CL_{int,T}$ values lower than 50 µl/min, RAF is limiting the contribution of active transport on CL_R, with low impact for high $CL_{int,T}$ values (Figure 1).
- For extremely high $CL_{int,T}$ values (i.e., > 589 µl/min), the impact of overall maturation of all system-specific parameters on CL_R is low (Figure 1).
- GFR and active tubular secretion are increasing proportionally with f_u (Figure 2A).
- When GFR is the main driver of CL_R (i.e., $CL_{int,T}$ is low), the maturation of the transporters capacity (mat_{TC}) has little impact on CL_R (Figure 2B).
- Disregarding the mat_{TC} could yield a difference of 41-303% in children younger than 1 year. This difference increases with decreasing f_u (Figure 2B).

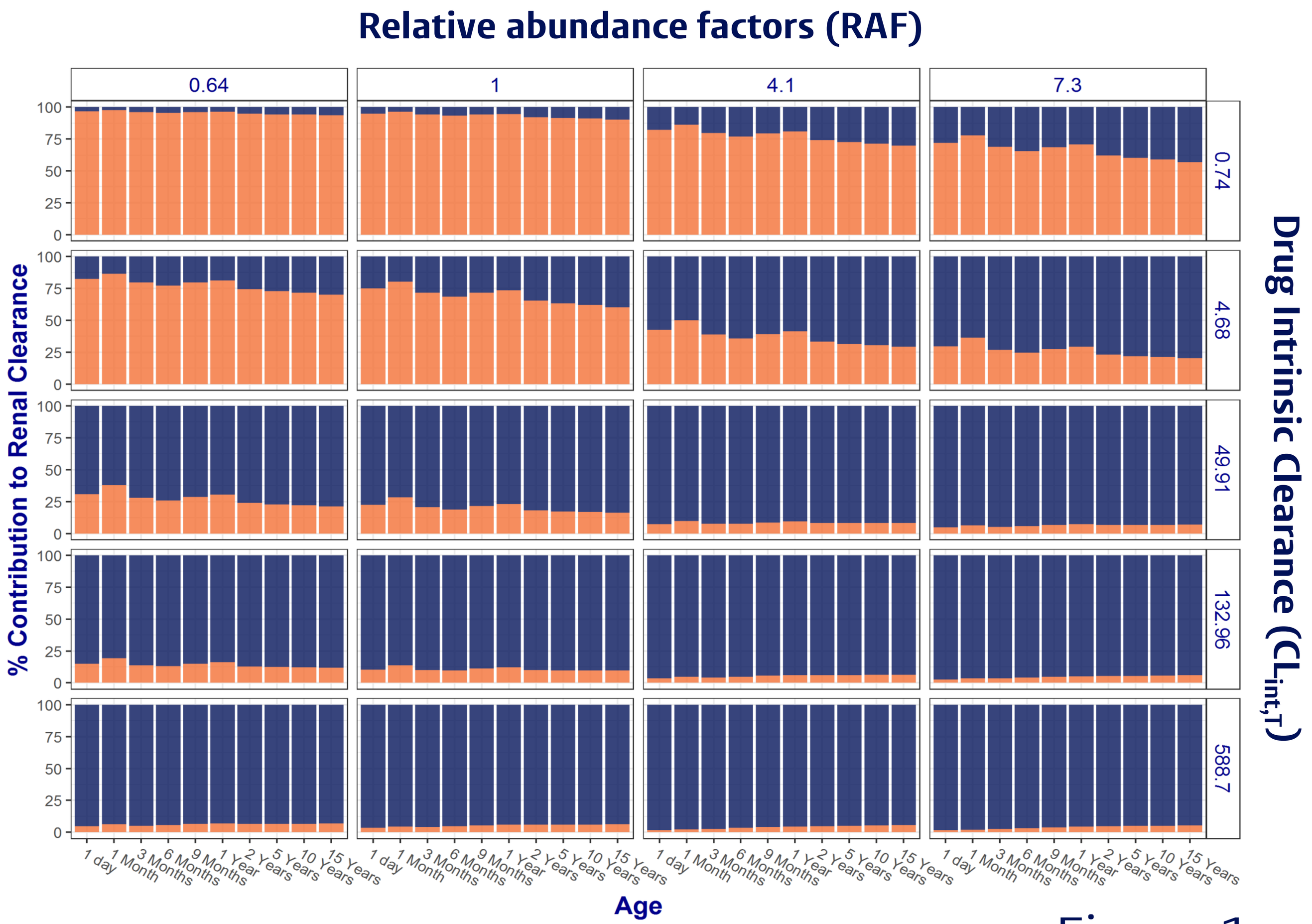

Figure 1

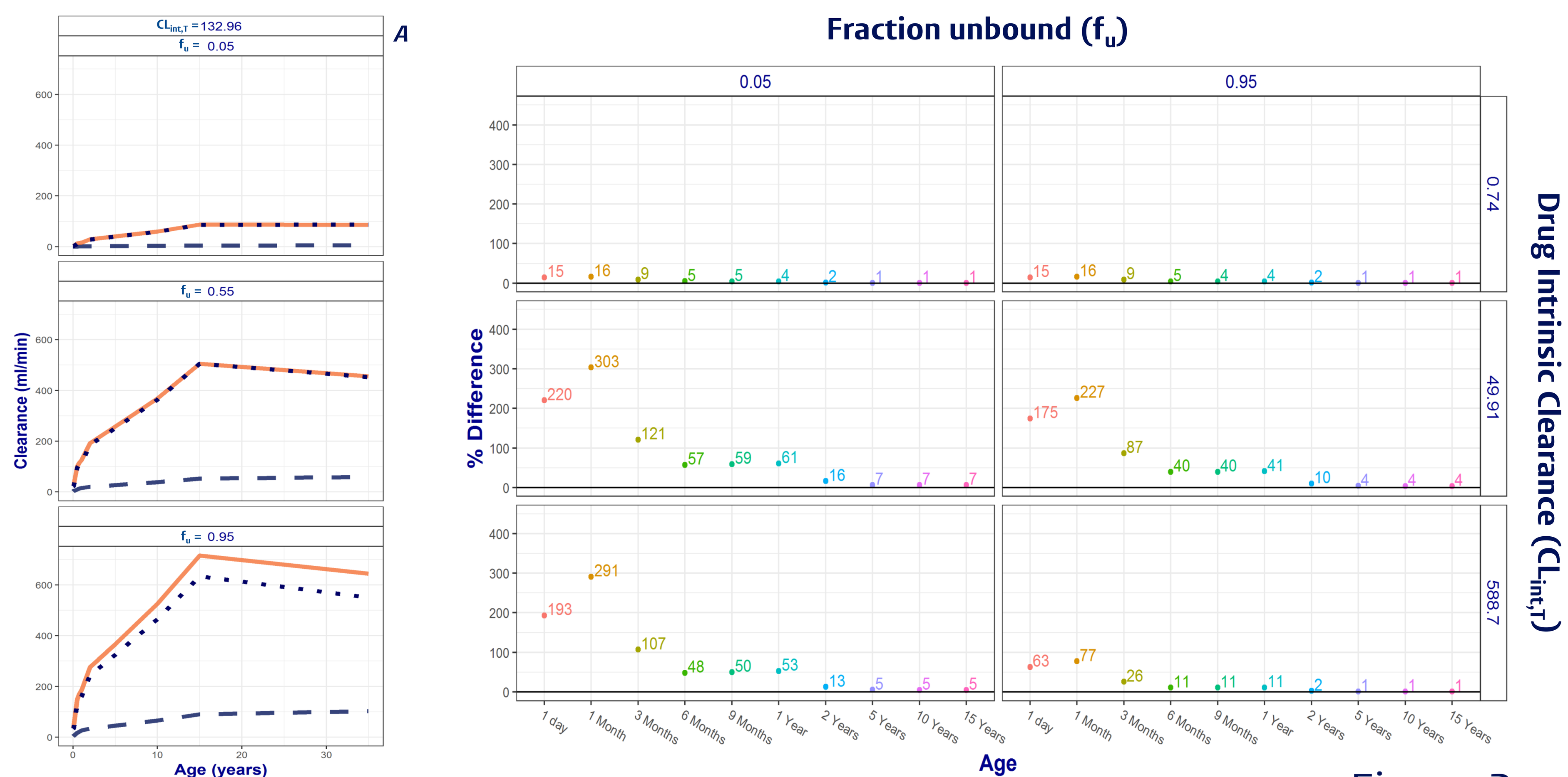

Figure 2

Figure 1 *- Contribution of GFR (**orange**) and active secretion (**blue**) as a percentage of the total renal clearance (CL_R). **Figure 2A** - Impact of overall maturation (age) and protein binding (f_u) on GFR (**blue** – dashed), active secretion (**black**– dotted) and total renal clearance (**orange** – solid) for $CL_{int,T}$, of 132.96 µl/min. **Figure 2B** - Impact of maturation of the transporters capacity (mat_{TC}) on CL_R versus age for low (0.74 µl/min), median (49.91 µl/min) and high (588.7 µl/min) $CL_{int,T}$ values and for low (0.05) and high (0.95) fraction unbound (f_u) with % difference representing the difference between CL_R with or without the mat_{TC} included.*

Universiteit Leiden
The Netherlands

LACDR

AFFILIATIONS

[1]Leiden Academic Center for Drug Research / Division of Pharmacology, Leiden University, The Netherlands
[2]Simcyp (A Certara Company), Blades Enterprise Centre, Sheffield, UK
[3]Manchester Pharmacy School, Manchester University, Manchester, UK
[4]St. Antonius Hospital, Nieuwegein, The Netherlands

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